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DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Food and Drug Administration

21 CFR Parts 210, 211, 820, and 1271

[Docket No. 97N-484S]

Suitability Determination for Donors of Human Cellular and Tissue-Based Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing new regulations to require manufacturers of human cellular and tissue-based products to screen and test the donors of cells and tissue used in those products for risk factors for and clinical evidence of relevant communicable disease agents and diseases. Human cellular and tissue-based products are products that contain or consist of human cells or tissues and that are intended for implantation, transplantation, infusion, or transfer. As part of this regulatory action, the agency is proposing to amend the current good manufacturing practice (CGMP) regulations that apply to human cellular and tissue-based products regulated as drugs, medical devices, and/or biological products to incorporate the new donor-suitability procedures into existing good manufacturing practice (GMP) regulations. The agency is taking this action to provide more appropriate oversight for the wide spectrum of human cellular and tissue-based products that are marketed now or may be marketed in the future. The agency's action would improve protection of the public health and increase public confidence in new technologies, while permitting significant innovation and keeping regulatory burden to a minimum.

DATES: Submit written comments on the proposed rule on or before (*insert date 90 days after date of publication in the Federal Register*). Submit written comments on the information

collection provisions on or before (*insert date 30 days after date of publication in the Federal Register*).

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit written comments on the information collection provisions to the Office of Information and Regulatory Affairs, OMB, New Executive Office Bldg., 725 17th St. NW., Washington, DC 20503, Attn: Wendy Taylor, Desk Officer for FDA.

FOR FURTHER INFORMATION CONTACT: Paula S. McKeever, Center for Biologics Evaluation and Research (HFM-17), Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852-1448, 301-827-6210.

SUPPLEMENTARY INFORMATION:

I. Introduction

FDA is in the process of establishing a comprehensive new system of regulating human cellular and tissue-based products. The term “human cellular and tissue-based products” encompasses an array of medical products derived from the human body and used for repair, reproductive, replacement, or other therapeutic purposes. Skin, tendons, bone, heart valves, and corneas have long been used as replacements for damaged or diseased tissues. Semen, ova, and embryos are transferred for reproductive purposes. Currently, some human cellular and tissue-based products are being developed for new therapeutic uses. For example, scientists are studying the use of manipulated human cells to treat viral infections, Parkinson’s disease, and diabetes, among other conditions and diseases. FDA’s new regulatory program will cover all of these products, including those currently regulated as “human tissue intended for transplantation” under part 1270 (21 CFR part 1270). (The proposed regulatory definition of a human cellular or tissue-based product, and exceptions from the definition, will be discussed in greater detail later in this document.)

In February 1997, the agency announced its regulatory plans in two documents: “Reinventing the Regulation of Human Tissue” and “A Proposed Approach to the Regulation of Cellular and Tissue-Based Products” (hereinafter referred to as the “proposed approach document”). FDA requested written comments on its proposed approach and, on March 17, 1997, held a public meeting to solicit information and views from the interested public (62 FR 9721, March 4, 1997).

In the **Federal Register** of May 14, 1998 (63 FR 26744), FDA proposed an establishment registration and product listing system for manufacturers of human cellular and tissue-based products (hereinafter referred to as the “proposed registration rule.”) The proposed registration rule was the first in a series of rules that the agency intends to propose to implement its new approach to these products. The proposed registration rule would require manufacturers of human cellular and tissue-based products to register with the agency, to list their products, and to submit regular updates. The rule defines “human cellular and tissue-based product,” sets out exceptions to this definition, e.g., vascularized human organs and certain minimally manipulated bone marrow, and describes certain types of establishment that would not be subject to the registration and listing requirement. In addition, the rule proposes criteria for regulation of a human cellular or tissue-based product solely under section 361 of the Public Health Service Act (the PHS Act) (42 U.S.C. 264), rather than as a drug, device, and/or biological product. Relevant portions of the proposed registration rule are discussed in this proposed rule as necessary, and the definitions contained in the proposed registration rule are reprinted in their entirety in section III.B.1 of this document.

As another step toward accomplishing its regulatory objectives, the agency recently issued a request for proposed standards and supporting data relating to certain stem-cell products (63 FR 2985, January 20, 1998).

FDA now proposes to require manufacturers of certain human cellular and tissue-based products to screen and test the donors of cells and tissues used in those products for risk factors for and clinical evidence of relevant communicable disease agents and diseases. The proposed

regulations are intended as safeguards to prevent the transmission of communicable diseases that may occur with the use of cells and tissues from infected donors.

In acting to increase the safety of the nation's supply of human cellular and tissue-based products, FDA is also seeking to avoid unnecessary regulation. Thus, consistent with the proposed approach document, the agency has tailored the proposed testing and screening requirements to the degree of communicable disease risk associated with the various types of human cellular and tissue-based products. The testing and screening for donors of cells and tissues that pose a high degree of communicable disease risk will be more extensive than for donors of cells and tissues with lesser risk. Where the risk is quite low (e.g., cells or tissues used autologously), FDA will recommend testing and screening, but will not require them; however, certain labeling will be required.

As outlined in the proposed approach document, the agency is implementing its regulatory plan for human cellular and tissue-based products in a step-by-step fashion. Following the publication of this proposed rule, the agency intends to propose current good tissue practice "CGTP" regulations to address concerns about the proper handling, storage, and processing of human cellular and tissue-based products. The donor-suitability regulations now being proposed would be placed in new part 1271, along with the regulations covering registration, CGTP, and other areas, e.g., establishment inspection and enforcement. Proposed part 1271 will eventually supersede part 1270, which contains current regulations governing infectious-disease testing, donor screening, and recordkeeping for human tissue intended for transplantation. At the completion of the rulemaking process, FDA intends to revoke part 1270.

II. Donor Suitability

A. Part 1270 and the Need for Expanded Donor-Suitability Requirements

In the early 1990's, serious issues arose about the safety of human tissue used for transplantation. Concern focused on the potential for disease transmission through the

transplantation of tissues from donors infected with the human immunodeficiency virus (HIV) or one of the hepatitis viruses. In 1993, FDA acted in response to this immediate need to protect the public health by issuing an interim rule requiring the donors of human tissue intended for transplantation to be screened and tested for HIV types 1 and 2, hepatitis B (HBV), and hepatitis C (HCV) (58 FR 65514, December 14, 1993). That rule, codified at part 1270, covered human tissue that was not regulated as a human drug, biological product, or medical device; reproductive tissue and several other categories of products were also excluded (§ 1270.3(j)). In response to comments submitted on the interim rule, FDA modified and clarified the requirements. In the **Federal Register** of July 29, 1997 (62 FR 40429), FDA issued a final rule replacing the interim rule (hereinafter referred to as the “tissue final rule”).

When it issued the regulations in part 1270, FDA envisioned replacing them, at a future date, with more extensive requirements with respect to infectious-disease control (58 FR 65514 at 65516). Consistent with these intentions, the agency is now proposing regulations that would expand on the current testing and screening requirements in two ways. First, the proposed regulations would increase the number of products covered by the screening and testing requirements. Second, the proposed regulations would require screening and testing for additional diseases. (The present rulemaking affects only the screening and testing components of part 1270. Other requirements will be the subject of future rulemaking, e.g., the requirement in § 1270.31 for written procedures and the enforcement provisions in part 1270 subpart D.)

Because of their nature as derivatives of the human body, all human cellular and tissue-based products pose a potential risk of transmitting communicable diseases. For example, HIV, HBV, and HCV have been detected in human tissue, including bone, skin, corneas, and semen. In proposing to establish a unified regulatory approach for human cellular and tissue-based products, the agency is responding to the concern about communicable disease transmission that is common to all such products. The proposed testing and screening provisions would be applicable to human cellular and tissue-based products that are regulated under section 201 of the Federal Food, Drug,

and Cosmetic Act (the act) (21 U.S.C. 321 *et. seq.*) and/or section 351 of the PHS Act (42 U.S.C. 262) as medical devices, drugs, and/or biological products. The proposed testing and screening provisions would also apply to human cellular products and products containing human reproductive cells or tissues, including some products not currently subject to Federal regulation. In addition, tissues currently regulated under part 1270 would be brought under the scope of the new regulations.

When part 1270 was issued as an interim rule, FDA was acting swiftly to counter the transmission of three serious disease agents, HIV, HBV, and HCV, by the transplantation of human tissue. In this rulemaking, the agency seeks to establish a more comprehensive system for preventing the spread of those and other diseases transmissible by implantation, transplantation, infusion, or transfer of human cellular and tissue-based products. The proposed regulation would require, except in certain limited situations, screening and testing for all “relevant” communicable disease agents and diseases. (The criteria for considering a disease to be “relevant” are discussed later in section III.C.1 of this document.) For example, FDA is now proposing to require that donors of tissue and cells be tested for syphilis and screened for transmissible spongiform encephalopathies (TSE) including Creutzfeldt–Jakob Disease (CJD). In addition, donors of viable, leukocyte-rich cells or tissues would be tested for human T-cell lymphotropic virus type I and type II (HTLV–I/II) and Cytomegalovirus (CMV), which are considered “cell-associated viruses.” FDA is proposing to require that donors of reproductive cells and tissue be tested for *Neisseria gonorrhea* and *Chlamydia trachomatis*, which have been transmitted through artificial insemination, and screened for sexually transmitted and genitourinary diseases that could contaminate reproductive cells and tissue during recovery and then be transmitted to the recipient of those cells or tissues and/or to the fetus.

B. Legal Authority

FDA is proposing to issue these new regulations under the authority of section 361 of the PHS Act. Under that section, FDA may make and enforce regulations necessary to prevent the

introduction, transmission, or spread of communicable diseases between the States or from foreign countries into the States. (See sec. 1, Reorg. Plan No. 3 of 1966 at 42 U.S.C. 202 for delegation of section 361 authority from the Surgeon General to the Secretary, Health and Human Services; see 21 CFR 5.10(a)(4) for delegation from the Secretary to FDA.) Intrastate transactions may also be regulated under section 361 of the PHS Act. (See *Louisiana v. Mathews*, 427 F. Supp. 174, 176 (E.D. La. 1977).)

Certain diseases are transmissible through the implantation, transplantation, infusion, or transfer of human cellular or tissue-based products derived from donors infected with those diseases. In order to prevent the introduction, transmission, and spread of such diseases, FDA considers it necessary to take appropriate measures to prevent the use of cells or tissues from infected donors. Thus, the agency is proposing that, prior to the use of most human cellular or tissue-based products, the manufacturer would be required to determine the suitability of the donor of cells or tissues based on the results of screening and testing for relevant communicable diseases. Under the proposed regulations, a donor who tests repeatedly reactive for a particular disease agent, or who possesses clinical evidence of or risk factors for such a disease, would be considered unsuitable, and cells and tissues from that donor would not ordinarily be used.

FDA's directive, under section 361 of the PHS Act, is to prevent the introduction, transmission, and spread of communicable diseases. Specifically, these regulations are intended to prevent the transmission of communicable disease through the implantation, transplantation, infusion, or transfer of human cellular or tissue-based products. However, as discussed in the proposed registration rule, all human cellular and tissue-based products pose some risk of carrying pathogens that could cause disease in recipients and family members or other close contacts of recipients, health care personnel, and other handlers of tissue. This broader concern for the spread of communicable disease is reflected in certain labeling requirements proposed in these regulations and in the criteria for identifying a relevant communicable disease. Although FDA recognizes that regulations exist that are specifically designed to protect employees who may come in contact

with infectious materials (see 29 CFR 1910.1030, 42 CFR 72.6, and 49 CFR 171.180), the agency does not consider its proposed regulations to be in conflict with those other regulations currently in effect. However, the agency has made an effort to be consistent with the terminology used in these other regulations, e.g., “Infectious Substances” and Biohazard legend.

Authority for the enforcement of section 361 of the PHS Act is provided by section 368 of the PHS Act (42 U.S.C. 271). Under section 368(a), any person who violates a regulation prescribed under section 361 of the PHS Act may be punished by imprisonment for up to 1 year, a fine of not more than \$1,000, or both (42 U.S.C. 271(a)). In addition, Federal District Courts have jurisdiction to enjoin individuals and organizations from violating regulations implementing section 361 of the PHS Act.

Under sections 501(a)(2)(B) and (h) and 520(f)(1) of the act (21 U.S.C. 351(a)(2)(B) and (h) and 360j(f)(1)), drugs and devices are subject to CGMP requirements designed to ensure, among other things, product safety. Currently, no specific CGMP regulations exist with respect to human cellular and tissue-based products regulated as drugs or devices that delineate testing and screening procedures for communicable diseases. (See parts 210 *et seq.* and 820 (21 CFR parts 210 and 820).) Nevertheless, FDA considers communicable disease testing and screening to be steps in the manufacturing process that are crucial to the safety of such products. As a result, FDA proposes to amend the existing CGMP regulations for drugs in parts 210 and 211 (21 CFR part 211) and the quality system regulations for devices in part 820 (21 CFR part 820), which include CGMP requirements, to incorporate the testing and screening provisions of proposed part 1271 subpart C. In proposing these amendments, FDA is relying on the authority provided by section 361 of the PHS Act to issue regulations to prevent the spread of communicable disease, as well as its authority under the act to issue CGMP regulations (21 U.S.C. 351(a)(2)(B) and (h) and 360j(f)(1)).

Under proposed § 210.1(c), the manufacturer of a human cellular or tissue-based product regulated as a drug or biological drug would be required to comply with the donor-suitability procedures in proposed part 1271, subpart C. Likewise, under proposed § 820.1, the manufacturer

of a human cellular or tissue-based product regulated as a device would be required to comply with the same procedures. (Existing regulations and policy determine whether a product is a drug, biological product, and/or device). If the manufacturer failed to follow the CGMP or quality system requirements, including the testing and screening procedures in proposed part 1271, the product would be adulterated under the act.

Section 375 of the PHS Act provides for Federal oversight of the nation's Organ Procurement and Transplantation Network and section 379 of the PHS Act authorizes the National Bone Marrow Donor Registry. The Health Resources and Services Administration (HRSA) currently administers both of these programs. Given HRSA oversight in these areas, vascularized human organs and minimally manipulated bone marrow (as defined in proposed § 1271.3(e)) for unrelated allogeneic use are specifically excluded from the proposed and final regulations on human cellular and tissue-based products.

III. Summary of the Proposed Regulation

A. Purpose and Scope (Proposed § 1271.1)

FDA is proposing that donor-suitability regulations would apply to all establishments covered by the proposed registration rule. In the proposed registration rule, FDA discussed its proposed system for regulating human cellular and tissue-based products. In particular, the agency proposed to distinguish between two groups of human cellular and tissue-based products: those that would be regulated solely under the authority of section 361 of the PHS Act ("361 products"), and those regulated under the act and/or section 351 of the PHS Act as drugs, medical devices and/or biological products as well as section 361 of the PHS Act.

Section 1271.1 of the proposed registration rule states that manufacturers of both 361 products and products regulated as drugs or devices and/or biological products under the act and/or section 351 of the PHS Act would be required to comply with the proposed registration and listing procedures. The criteria for regulation of a human cellular or tissue-based product as a 361 product

are set out in § 1271.10 of the proposed registration rule. Section 1271.20 of the proposed registration rule sets out exceptions from the registration and listing requirements.

FDA is now making several modifications to proposed §§ 1271.1, 1271.10, and 1271.20 as they appeared in the proposed registration rule and is proposing a new § 1271.15. To improve clarity, FDA has divided section 1271.1 into separate paragraphs on scope and purpose and has added cross-references to other pertinent regulations. FDA has also changed the heading of proposed § 1271.10 to “Establishments subject to this part; criteria for regulation of human cellular and tissue-based products solely under section 361 of the PHS Act.” The phrase “nontissue or noncellular” has been removed from proposed § 1271.10(c). Proposed § 1271.10(d) has been reorganized, although its meaning has not changed. Proposed § 1271.10 now describes human cellular and tissue-based products regulated solely under section 361 of the PHS Act as those products that: Are minimally manipulated, are not promoted or labeled for any use other than a homologous use, are not combined with or modified by the addition of any component that is a drug or a device; and either do not have a systemic effect or have a systemic effect and are for autologous use, are for a family-related allogeneic use, or are for reproductive use. FDA expects that comments on the four criteria in proposed § 1271.10 will be submitted in response to the proposed registration rule, and foresees that each of the four criteria will be modified for greater clarity. For example, the agency is considering clarifying or modifying the term “systemic effect” in proposed § 1271.10(d) because of potential ambiguities. FDA is concerned that products that have local metabolic effects, e.g., neurons used to replace or supplement neurons in the brain, warrant regulation under the act and/or section 351 of the PHS Act. The agency invites comments on whether “systemic effect” adequately characterizes those products that warrant the more stringent level of regulation or whether another term or terms would more accurately describe such products.

FDA is proposing a new § 1271.15 to describe those products that would be regulated under the act and/or section 351 of the PHS Act and to reference the subparts of part 1271 that will be applicable to those products.

FDA is also modifying proposed §§ 1271.1, 1271.10, and 1271.20 so that they refer not simply to registration and product listing requirements but to all of the requirements that will be contained in part 1271 when rulemaking for the entire part is complete. With these changes, the regulatory framework that was described in the proposed approach document and developed in the proposed registration rule would be extended, as intended, to cover donor-suitability requirements now being proposed as well as other requirements to be proposed later. The agency is seeking to craft the modifications to these sections to obviate the need for further adjustments in later rulemaking. To that end, the new language refers to compliance “with the other requirements contained in this part.”

FDA intends that the procedures in part 1271 that would apply to human cellular and tissue-based products regulated as drugs, devices and/or biological products are the proposed registration and listing procedures, the donor-suitability procedures now being proposed, and the CGTP procedures to be proposed in the future. Therefore, the agency is now proposing to modify proposed § 1271.1 to add the statement that manufacturers of human cellular and tissue-based products regulated under the act and/or section 351 of the PHS Act are required to comply with the donor-suitability procedures and the CGTP procedures in part 1271 in addition to all other applicable regulations.

B. Definitions (Proposed § 1271.3)

1. Definitions Contained in the Proposed Registration Rule

Section 1271.3(a) through (h) of the proposed registration rule contain definitions of terms used in the registration and listing regulations. Because some of the terms defined in the proposed registration rule are used in the donor-suitability regulations now being proposed, the agency is

reprinting proposed § 1271.3(a) through (h) as follows to facilitate understanding of the rule now being proposed.

(a) *Autologous use* means the implantation, transplantation, infusion, or transfer of a human cellular or tissue-based product back into the individual from whom the cells or tissue comprising such product were removed.

(b) *Establishment* means a place of business under one management, at one general physical location, that engages in the manufacture of human cellular or tissue-based products. The term includes, among others, facilities that engage in contract manufacturing services for a manufacturer of human cellular or tissue-based products. The term also includes any individual, partnership, corporation, association, or other legal entity engaged in the manufacture of human cellular or tissue-based products, except that an individual engaged solely in the procurement or recovery of cells or tissues or under contract to a registered establishment is not required to independently register.

(c) *Family-related allogeneic use* means the implantation, transplantation, infusion, or transfer of a human cellular or tissue-based product into a first-degree blood relative of the individual from whom cells or tissue comprising such product were removed.

(d) *Homologous use* means the use of a cellular or tissue-based product for replacement or supplementation and:

(1) For structural tissue-based products, occurs when the tissue is used for the same basic function that it fulfills in its native state, in a location where such structural function normally occurs; or

(2) For cellular and nonstructural tissue-based products, occurs when the cells or tissue is used to perform the function(s) that they perform in the donor.

(e) *Human cellular or tissue-based product* means a product containing human cells or tissues or any cell or tissue-based component of such a product. The following products are not considered human cellular or tissue-based products and establishments that manufacture only one or more of the following would not be subject to the registration or listing provisions of this part:

(1) Vascularized human organs for transplantation;

(2) Whole blood or blood components or blood derivative products subject to listing under part 607 of this chapter;

(3) Secreted or extracted human products, such as milk, collagen, and cell factors;

(4) Minimally manipulated bone marrow;

(5) Ancillary products used in the propagation of cells or tissues; or

(6) Cells, tissues or organs derived from animals.

(f) *Manufacture* means, but is not limited to, any or all steps in the recovery, screening, testing, processing, storage, labeling, packaging, or distribution of any human cellular or tissue-based product.

(g) *Minimal manipulation* means: (1) For structural tissue, processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement; and

(2) For cells or nonstructural tissues, processing that does not alter the relevant biological characteristics of cells or tissues.

(h) *Transfer* means the placement of human reproductive cells or tissues into a human recipient.

Since proposing the previous definitions, FDA has reconsidered the definition in proposed § 1271.3(e) of “human cellular or tissue-based product,” and has determined that it is too broad. For example, the definition might be construed to include many in vitro diagnostic products. The agency is adding language to the proposed definition to clarify that the products covered by the definition (and thus by these proposed regulations) are those that are intended for implantation, transplantation, infusion, or transfer into a human recipient. The agency is also adding language to specifically exclude in vitro diagnostic products as defined in 21 CFR 809.3(a) from the definition of human cellular or tissue-based product. In addition, the agency is deleting the reference in § 1271.3(e) to the registration and listing provisions of part 1271. Minimally manipulated bone marrow has been clarified by adding “for homologous use and not combined with or modified by the addition of any component that is a drug or a device.” Also, the agency is clarifying that, although secreted or extracted human products such as milk, collagen, and cell factors are not

considered to meet the definition of human cellular or tissue-based product, semen is considered a human cellular or tissue-based product because it contains germ cells. The definition also contains several other minor clarifications and corrections.

2. New Definitions

The agency is now proposing to define additional terms and to list them in § 1271.3(i) through (ee). The agency intends to place all definitions relevant to proposed part 1271 in proposed § 1271.3. Thus, in subsequent rulemakings, the agency may propose to define more terms in that section.

Many of the terms now proposed to be defined in proposed § 1271.3 are currently defined in § 1270.3. In several instances, the definition now being proposed is the same as that in § 1270.3 or is only modified slightly for clarity, e.g., “donor” and “responsible person” in proposed § 1271.3(n) and (w), respectively. Although the proposed definitions of colloid and crystalloid remain substantially the same as in § 1270.3(c) and (e), the agency specifically requests comments on the appropriateness of these definitions, including whether it is appropriate to define these terms in the regulations.

The definitions of some other terms (e.g., donor medical history interview and physical assessment) have been significantly modified to accommodate the broader range of infectious diseases covered by this proposed regulation. Additional terms are newly defined in proposed § 1271.3 (Biohazard legend, directed donor, embryo, gamete, relevant communicable disease agent or disease, urgent medical need, xenotransplant, and close contact). Where relevant, proposed definitions are discussed as follows, with the requirements to which the defined terms relate.

The definition of “summary of records” in proposed § 1271.3(x) is a modification of the definition of the same term in § 1270.3(w). As in § 1270.3(w), the agency proposes to define “summary of records” as containing a list of all tests performed for relevant communicable disease agents and the results of those tests, and the name and address of the establishment that made the donor-suitability determination. However, FDA has recently received comments from

manufacturers of human tissue intended for transplantation on other aspects of the definition of “summary of records” in § 1270.3(w). These comments assert that, because a processor or distributor may use multiple testing laboratories, the requirement in § 1270.3(w) that a summary of records contain the identity of the testing laboratory is unduly burdensome; similar objections were raised to the requirement for listing all relevant medical records reviewed. Such information, it was asserted, would be available from the establishment that made the donor-suitability determination. FDA has considered these concerns, and is proposing a new, less burdensome definition. Under the proposed definition, the summary of records would be redefined as: (1) A statement that communicable disease testing was performed by a laboratory or laboratories certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA); (2) a listing and interpretation of the results of all communicable disease tests performed; (3) a statement describing the types of records which may have been reviewed as part of the relevant medical records; and (4) the name and address of the establishment determining the suitability of the donor of cells or tissues. Upon request by FDA, or other interested persons, the establishment that made the donor-suitability determination will be expected to promptly furnish the name and address of the testing laboratory and a list of all relevant medical records reviewed.

C. General Requirements

1. Determination of Donor Suitability (Proposed § 1271.50)

Proposed § 1271.50 sets out the fundamental requirement of these proposed regulations: The donor-suitability determination. Except in certain specified situations, a human cellular or tissue-based product may not be implanted, transplanted, infused, or transferred until the donor of the cells or tissue for the product has been determined to be suitable.

The determination of whether a donor is suitable or unsuitable would be made by a responsible person, as defined in proposed § 1271.3(w), and would be based on the results of required donor screening and testing. “Donor screening” refers to a review of the donor’s relevant medical

records, as defined in proposed § 1271.3(v), for information about the donor that might indicate past or present infection or risk factors for a relevant communicable disease agent or disease.

“Donor testing” refers to performing laboratory tests on a specimen collected from the donor, generally a blood sample, to determine whether the donor has been exposed to or is infected with a relevant communicable disease agent.

Both aspects of the donor-suitability determination are vital. A donor may be determined to be suitable only if test results are negative or nonreactive and screening shows the donor to be free from risk factors for and clinical evidence of infection due to relevant communicable disease agents and diseases. Conversely, if either donor screening or donor testing indicates the presence of a relevant infectious agent, or risk factors therefor, then the potential donor must be determined to be unsuitable.

Proposed § 1271.3(y) contains a two-part definition of the term “relevant communicable disease agent or disease.” Section 1271.3(y)(1) lists those disease agents and diseases that are specifically identified in §§ 1271.75 and 1271.85 as relevant communicable disease agents and diseases for which the agency is proposing to require donor screening and/or testing. These are: HIV, types 1 and 2; HBV; HCV; TSE; *Treponema pallidum*; HTLV, types I and II; CMV; *Chlamydia trachomatis* and *Neisseria gonorrhea*. In some instances, FDA has identified a disease agent or disease as relevant for a particular type of cells or tissue-based product; this distinction is reflected in the proposed testing and screening requirements in proposed §§ 1271.75 and 1271.85.

The second part of the definition describes the criteria for a communicable disease agent or disease to be considered “relevant,” and covers diseases not specifically listed in § 1271.3(y)(1). First, for a communicable disease agent or disease to be “relevant,” its prevalence among donors would have to be sufficient to warrant screening or testing of all donors. Second, there would need to be a risk of transmission of the disease agent or disease by a human cellular or tissue-based product, either to the recipient of the product or to those people who may handle or otherwise come in contact with the product, such as medical personnel. Third, the health risks, measured

by morbidity and mortality, posed by the disease would need to be significant. For example, HIV, HBV, HCV, and *Treponema pallidum*, which are listed in § 1271.3(y)(1), all pose significant health risks. In contrast, although *Ureaplasma urealyticum*, *Mycoplasma hominis*, and Streptococci are organisms that have been transmitted through artificial insemination procedures, they exist in a great number of healthy, sexually active adults and their pathogenicity to the recipient of reproductive cells or tissue is of questionable clinical significance. Thus, FDA does not consider them to be relevant communicable diseases or disease agents at this time for the purpose of this regulation. Finally, for a disease or disease agent to be considered “relevant,” appropriate screening measures would need to have been developed and/or an appropriate FDA-licensed, approved, or cleared screening test for donor specimens would need to be available.

Should a new relevant communicable disease agent or disease arise or be identified, the agency would consider manufacturers to be required, under proposed § 1271.75(a), to screen donors for the disease and, under proposed § 1271.80(a), to test donor specimens for the disease agent, even if the disease agent or disease is not specified in proposed §§ 1271.3(y), 1271.75, or 1271.85. The agency intends to issue guidance in the future to interpret the term “relevant communicable disease agent or disease,” when additional agents or diseases arise or are identified that meet the definition under proposed § 1271.3(y).

2. Records of Donor Suitability Determination (Proposed § 1271.55)

Proposed § 1271.55 incorporates requirements that are now found in (§§ 1270.21(e) and 1270.33(d) and (f)). Additional recordkeeping requirements based on other regulations in part 1270 will be proposed in the future, as part of CGTP’s.

Under proposed § 1271.55, manufacturers would be required to ship a human cellular or tissue-based product accompanied by documentation of the donor-suitability determination. This requirement would apply to a human cellular or tissue-based product from a donor determined to be suitable as well as to a product from a donor determined to be unsuitable and made available for use under the provisions of proposed § 1271.65(b), (c), or (d). Manufacturers would be required

to include in the documentation a copy of the donor's relevant medical records, as defined in proposed § 1271.3(v), results of testing required under §§ 1271.80 and 1271.85, and the name and address of the establishment that made the donor-suitability determination. Alternatively, the documentation may consist of a summary of records, as defined in proposed § 1271.3(x). Additional required documentation would include a statement whether, based on a review of the results of donor screening and testing, the donor has been determined to be suitable or unsuitable. In the interest of confidentiality, the agency is proposing to require that the donor's name be deleted from the documentation of the donor's suitability determination that accompanies the product.

FDA recognizes the potentially sensitive nature of information about a human cell or tissue donor that may be contained in the donor's relevant medical records. Nothing in this proposed rule is intended to modify any currently applicable Federal, State, or local regulations regarding confidentiality. With respect to the agency's handling of personal medical information, the regulations in part 20 (21 CFR part 20) will continue to apply (see § 20.63).

Proposed § 1271.55(b) would impose record-retention requirements on the establishment that generates records used in determining donor suitability and on the establishment that makes the donor-suitability determination. These records must be made available for authorized inspection by or upon request from FDA. Records that can be readily retrieved from another location by electronic means would be considered "retained." FDA envisions that various methods of recordkeeping could be employed to meet the terms of § 1271.55(b), so long as suitable reader and photocopying equipment were readily available. For example, records might be retained electronically, as original paper records, or as true copies, such as photocopies, microfiche, or microfilm.

Proposed § 1271.55(b) would require that records be retained at least 10 years after the date of implantation, transplantation, infusion, or transfer of the product. If that date is not known, however, then records would be retained at least 10 years after the product's distribution, disposition, or expiration, whichever is latest.

The agency notes that, given concerns about TSE transmission from dura mater, it may be prudent to hold records relating to donations of dura mater for longer than 10 years, although the optimal period is not known at this time. The latency period between receipt of a dura mater graft and onset of TSE has been reported to be as long as 16 years (Morbidity and Mortality Weekly Report, 46:1066, November 14, 1997). If new information should be obtained in the future about TSE, then review of the original screening and testing information about dura mater donors could be invaluable. The agency requests comments on whether records relating to donors of dura mater should be required to be held for a period longer than 10 years and what that period should be.

3. Quarantine Pending Determination of Donor Suitability (Proposed § 1271.60)

In order to prevent the use of human cellular and tissue-based products prior to a donor-suitability determination, § 1271.60 proposes requirements for quarantine. “Quarantine” is defined in proposed § 1271.3(t) as “the storage or identification of a human cellular or tissue-based product, in order to prevent improper release, in a physically separate area clearly identified for such use, or through use of other procedures, such as automated designation.”

As provided in proposed § 1271.60, manufacturers would be required to keep human cellular and tissue-based products in quarantine, and clearly identify such products as being in quarantine, until completion of the donor-suitability determination. A manufacturer who ships a product before it is available for release or distribution (as in the case of shipment by the procurer to the processor) would be required to ship the product under quarantine and accompanied by records identifying the donor, indicating that the donor-suitability determination has not been completed, and stating that the product may not be implanted, transplanted, infused, or transferred until completion of the donor-suitability determination. Donor identification may be accomplished by assigning a donor number.

4. Quarantine and Disposition of Human Cellular or Tissue-based Product From an Unsuitable Donor (Proposed § 1271.65)

If a donor is determined to be unsuitable, then under proposed § 1271.65 the manufacturer would be required to keep in quarantine any human cellular or tissue-based product from that donor. In this situation, quarantine would require physical separation of the product from all other products until it is destroyed, or until it is used under the provisions of proposed § 1271.65(b), (c), or (d).

Proposed § 1271.65 (b) sets out the limited circumstances in which the proposed regulations would not bar the implantation, transplantation, infusion, or transfer of human cellular and tissue-based products from unsuitable donors. In three situations, the agency is proposing that the recipient and his or her physician may decide whether to use the human cellular or tissue-based product.

The first exception is for family-related allogeneic use. Family-related allogeneic use is defined in § 1271.3(c) of the proposed registration rule as the implantation, transplantation, infusion, or transfer of a human cellular or tissue-based product into a first-degree blood relative of the individual from whom cells or tissue comprising such product were removed. Under the second exception, a person could choose to receive a product containing reproductive tissue from a directed donor who had been determined to be unsuitable. (Proposed § 1271.3(m) defines “directed donor” as a living person who is the source of cells or tissue designated for a specific potential recipient of a human cellular or tissue-based product.) The third exception is for cases where an urgent medical need exists and is documented. Urgent medical need is defined in proposed § 1271.3(z) as the situation where no comparable human cellular or tissue-based product from a suitable donor is available and, without the product, the recipient is likely to suffer serious morbidity.

However, use in each of these circumstances is conditioned on compliance with certain safeguards. First, in order to protect those people who may handle the product, the manufacturer would be required to label such products with a Biohazard legend. (A Biohazard legend is shown in proposed § 1271.3(i) and is used to mark products that present “a known or suspected relevant

communicable disease risk.’’) Second, the manufacturer of the product would be responsible for documenting that: (1) The physician using the product was notified of the results of testing and screening, (2) the physician authorized the use of the product, (3) the physician agreed to explain the communicable disease risks associated with the product to the recipient or the recipient’s legally authorized representative, and (4) the physician agreed to obtain from the recipient or the recipient’s legally authorized representative consent to use the product. In proposing these exceptions that would not prohibit, in certain cases, the use of products from an unsuitable donor, it is FDA’s intention to delegate to the potential recipient and his or her physician the responsibility for comparing the relative risks and benefits. The agency specifically seeks comment on the scope of the exceptions and the proposed safeguards that FDA has crafted. For example, does the exception for directed reproductive tissue donors provide a reasonable accommodation for a woman who wishes to choose the genetic father of her child? Should the exception be further broadened to permit a woman to select an anonymous donor with a known high risk behavior or, conversely, does the exception provide sufficient protection for the woman and her potential child?

FDA recognizes that, just as there may be urgent medical situations that might justify the use of a human cellular or tissue-based product from an unsuitable donor, so the need may arise to use a human cellular or tissue-based product before the donor-suitability determination has been completed. Proposed § 1271.65(c) sets out the limited, emergency circumstances in which the proposed regulations would not prohibit the implantation, transplantation, infusion, or transfer of such a product. The emergency provisions of § 1271.65(c) are similar to those in § 1271.65(b), with some modifications appropriate to the different characteristics of the situation. In particular, a product made available for use pending completion of the donor-suitability determination must be accompanied by information on the status of the required screening and testing. In addition, § 1271.65(c) includes the requirement that the donor-suitability determination be completed during or after the use of the product, and that the manufacturer inform the physician of the results of that determination.

Under proposed § 1271.65(d), nonclinical uses of a human cellular or tissue-based product from an unsuitable donor would not be prohibited, e.g., use for educational or research purposes. A manufacturer would be required to label a product used under the provisions of § 1271.65(c) as “For Nonclinical Use Only” and with the Biohazard legend shown in proposed § 1271.3(i).

D. Donor Screening (Proposed § 1271.75)

The determination of donor-suitability is based on the results of two different evaluations: Screening and testing. Donor screening involves the review of a variety of possible sources of information about the donor that might indicate that the donor is at risk for or exhibits clinical evidence of infection due to a relevant communicable disease.

1. General Requirements

The requirements for donor screening are in proposed § 1271.75. Under proposed § 1271.75(a), the manufacturer would be required to review the relevant medical records of a donor of cells or tissue for a human cellular or tissue-based product for risk factors for and clinical evidence of relevant communicable disease agents and diseases. Relevant medical records are defined in proposed § 1271.3(v) as a collection of documents that includes a current donor medical history interview as defined in proposed § 1271.3(o); a current report of the physical assessment as defined in proposed § 1271.3(r) of a cadaveric donor or a physical examination of a living donor; and, if available, laboratory test results, medical records, coroner and autopsy reports, and records or other information received from any source pertaining to risk factors for relevant communicable disease. (The proposed definitions for “relevant medical records,” “donor medical history interview,” and “physical assessment” have been broadened to refer not only to HIV and hepatitis but instead to “relevant communicable disease;” in other respects, except as otherwise noted, these definitions are substantially the same as those currently in § 1270.3.)

Under proposed § 1271.3(v), risk factors for communicable disease may include social behavior, clinical signs and symptoms of a relevant communicable disease, and treatments related

to medical conditions suggestive of risk for a relevant communicable disease. Consistent with the approach taken in part 1270, the proposed regulations do not specify risk factors, as these may change as knowledge of communicable diseases grows. FDA, together with CDC, is reviewing the risk factors for transmission of relevant communicable diseases in light of current scientific knowledge. Based on the results of the review, FDA plans to specifically describe in a guidance document risk factors and screening information to assist manufacturers in complying with the regulation. A notice announcing the availability of a draft guidance document for public comment will be published in the **Federal Register**. The notice will provide instructions for obtaining copies of the draft guidance document by mail, facsimile, and the Internet using the World Wide Web. FDA plans to issue a final guidance document on or about the time of issuance of the final rule.

Under proposed § 1271.75(d), an abbreviated screening procedure may be used for a living donor who returns to make subsequent donations and who has already been screened under § 1271.75(a) and (b). This abbreviated screening would determine whether any changes had occurred in the donor's medical history since the previous donation that would make the donor unsuitable, and would require documentation of those changes. A complete donor-suitability determination procedure would be required at least once every 6 months.

Under proposed § 1271.3(o), a "donor medical history interview" means a documented dialogue with the donor, if the donor is living. If the donor is not living or is unable to participate in the interview, the interview takes place with an individual or individuals who are knowledgeable about the donor's medical history and relevant social behavior, such as the donor's next of kin, the nearest available relative, a member of the donor's household, an individual with an affinity relationship, and/or the primary treating physician. With respect to relevant social behavior, the definition states that the interview includes questions about whether or not the donor met certain descriptions or engaged in activities or behaviors considered to place the donor at increased risk for a relevant communicable disease.

The current regulations on human tissue intended for transplantation contain an exception from the requirement for a donor medical history interview for corneas obtained under legislative consent; i.e., in accordance with a State law that allows the medical examiner or coroner to procure corneal tissue without the consent of the donor's next of kin (§ 1270.21(g)). In response to numerous comments and discussions about the tissue interim rule, FDA acknowledged the need for flexibility in the procurement of corneal tissue under legislative consent, and modified the regulations to accept as sufficient a physical assessment of the donor in the absence of a donor medical history interview (62 FR 40429 at 40437).

The regulations now being proposed do not contain an exception from the donor medical history interview for corneas procured under legislative consent. FDA recognizes that, when corneal tissue is procured without the consent of the donor's next of kin, a donor medical history interview with the donor's next of kin does not necessarily occur. However, the agency notes that the proposed definition of donor medical history interview would permit the interview to be conducted with an individual knowledgeable about the donor's medical history and relevant social behavior (e.g., primary treating physician) and would not require an interview with the next of kin. For this reason, FDA considers that the proposed regulation and State laws on legislative consent may coexist, and does not intend at this time to preempt those laws. The agency requests that affected parties submit specific, detailed comments on any potential conflicts that might make it impossible to comply with both this regulation and State laws on legislative consent.

Requiring a donor medical history interview for corneas obtained under legislative consent is necessary to ensure that the risk of communicable disease transmission is appropriately assessed. To prevent the transmission of communicable disease, adequate donor screening measures are necessary, even when approved tests are available.

The necessity of adequate screening for TSE illustrates the importance of the donor medical history interview. The regulations now being proposed would require TSE screening for all cell and tissue donors and, in the case of dura mater donors, a post-mortem physical assessment for

TSE. (In contrast, current regulations on human tissue intended for transplantation contained in part 1270 do not require screening or testing for TSE.) Two recent possible transmissions of TSE by corneal tissue have been reported in Japan and Germany. In addition, three potential CJD transmissions have been reported in the United Kingdom, where corneas and sclera from a donor subsequently determined to have CJD were transplanted into, and then removed from, three recipients (Ref. 20). Recent cognitive changes and abnormalities in speech and gait are possible indications of TSE. These and other behavioral changes that a cell or tissue donor might exhibit prior to donation would be expected to be uncovered in the donor medical history interview, but would be less likely to turn up during other parts of the screening process.

2. Specific Communicable Disease Screening Requirements

Proposed § 1271.75(a)(1) states that the relevant medical records for a cell or tissue donor shall be reviewed for risk factors for and clinical evidence of infection due to relevant communicable disease agents and diseases. Proposed § 1271.75(a)(1) specifically lists HIV, HBV, HCV, and TSE as relevant communicable disease agents and diseases for which such screening is required. These four disease agents and diseases are listed as the “minimum” for which screening would be required; should a new relevant communicable disease arise or be identified, the agency would consider manufacturers to be required, under proposed § 1271.75(a)(1), to screen for the new disease as well.

Special concerns arise with respect to donors of reproductive cells or tissue, when those cells or tissue are recovered through methods that could lead to the transmission of sexually transmitted and genitourinary diseases. Accordingly, under proposed § 1271.75(b), if those methods are used, donor screening would be required for risk factors for and clinical evidence of infection due to sexually transmitted and genitourinary diseases. Certain methods of recovery, e.g., laparoscopy to recover oocytes, are not directly connected with the transmission of sexually transmitted and genitourinary diseases, and would not trigger this requirement.

Special concerns also arise with respect to potential donors who have received xenotransplants. Xenotransplantation is the transplantation of live cells, tissues, and/or organs between different species, such as from a baboon or pig to a human. Because transplantation necessitates disruption of the recipient's usual protective physical immunologic barriers, xenotransplantation may facilitate transmission of known and as yet unrecognized agents to humans. These can include unknown retroviruses, which may remain latent for a period of time before causing clinically recognized disease. Concerns about the potential infectious disease and public health risks associated with xenotransplantation have been discussed at two recent FDA meetings (Xenotransplantation Advisory Subcommittee of the Biologic Response Modifier Advisory Committee, December 17, 1997, and Blood Products Advisory Committee, March 19, 1998).

Cells or tissue from a xenotransplant recipient could potentially contain infectious agents transmitted by the xenotransplant. In addition, the cells or tissues of a person who has been a close contact of a xenotransplant recipient could contain infectious agents originating from the xenotransplant. Because of the potential severity of the risk associated with these situations, the agency is proposing to require, in § 1271.75(a)(2), that medical records be reviewed to determine whether a potential donor of cells or tissue has received a xenotransplant or has been a close contact of a xenotransplant recipient. If so, the donor would be determined to be unsuitable under proposed § 1271.75(c).

FDA is proposing to define "xenotransplantation" in § 1271.3(aa) as any procedure that involves the use of live cells, tissues, or organs from a nonhuman animal source, transplanted or implanted into a human, or used for ex vivo contact with human body fluids, cells, tissues, or organs that are subsequently given to a human recipient. Nonliving biological products or materials from animals, such as porcine heart valves, porcine insulin, and bovine serum albumin, have been used clinically for decades and would not be considered xenotransplantation products for purposes of these regulations. "Close contacts" of a xenotransplant recipient would be defined

in proposed § 1271.3(bb) as household members and others with whom the recipient participates in activities that could result in exchanges of bodily fluids.

E. Donor Testing

In addition to donor screening, the analysis of donor test results is necessary for a donor-suitability determination. Laboratory tests conducted on specimens collected from a cell or tissue donor can indicate whether the donor has evidence of infection due to a relevant communicable disease agent or disease. Proposed § 1271.80 sets out the general requirements for donor testing. Disease- and product-specific requirements are in proposed § 1271.85.

FDA notes that the proposed regulations employ the word “screening” in two different contexts. In proposed §§ 1271.80 and 1271.85, “screening test” refers to a laboratory test to determine exposure to or presence of a relevant communicable disease agent. The agency has used the term “screening test” in the past, e.g., § 1270.21, and considers it to be the generally recognized term in the industry and medical community for this type of initial test. Other sections of the proposed regulations, e.g., proposed § 1271.75, use the term “donor screening” to refer to the review of the donor’s relevant medical records, as defined in proposed § 1271.3(v). This use of “donor screening” is consistent with part 1270 and with usage by the industry and medical community.

1. General Requirements (Proposed § 1271.80)

FDA proposes in § 1271.80(a) to require that a donor specimen be tested for evidence of infection due to relevant communicable disease agents and diseases, which would include, at a minimum, those specified in proposed § 1271.85. Proposed § 1271.80(a) states that a specimen from the mother of a fetal or neonatal donor would be acceptable for testing. The proposed regulation also specifically notes that the purpose of testing is to adequately and appropriately reduce the risk of transmission of relevant communicable diseases.

Proposed § 1271.80(b) addresses the timing of the collection of a donor specimen for testing. The agency proposes to require that the donor specimen be collected at the time of recovery of cells or tissue from the donor or within 48 hours after recovery. The agency is concerned that a specimen collected prior to donation may not accurately reflect the donor's actual exposure to a relevant communicable disease at the time of donation. However, the agency recognizes that there may be certain instances in which it would be preferable to analyze a donor specimen to determine donor suitability in advance of recovery of cells or tissue. For that reason, the agency proposes that, for living donors, a specimen may be collected up to 7 days prior to recovery if:

- (1) Recovery of the cells or tissue involves invasive procedures or substantial risk to the donor;
- (2) implantation, transplantation, infusion, or transfer of the recovered cells or tissue is necessary before results of testing performed on a specimen collected at the time of recovery or post recovery would be available; or
- (3) extensive processing of the recovered cells or tissue is necessary before results of testing performed on a specimen collected at the time of recovery or post recovery would be available.

The agency recognizes that its proposed requirement on the timing of collection of donor specimens differs from testing practices currently followed by various industry members, and specifically requests comments on this proposal. Any comments that propose an alternative time period should explain how the proffered alternative balances the agency's concern about the spread of communicable disease with the practical concerns relating to the coordination of donor testing and donation.

Under proposed § 1271.80(c), testing would be required to be performed using FDA-licensed, approved, or cleared donor screening tests in accordance with the manufacturer's instructions, to adequately and appropriately reduce the risk of transmission of relevant communicable disease agents or diseases. Proposed § 1271.80(c) contains a proviso with respect to *Chlamydia trachomatis* and *Neisseria gonorrhea*, for which testing of certain donors of reproductive cells and tissues would be required under proposed § 1271.85(c). At this time there are no FDA-licensed, approved, or

cleared donor screening tests available for those two disease agents. However, the agency considers that testing for the disease agents is essential to prevent their spread, and that the use of tests labeled for the detection of those organisms in an asymptomatic, low-prevalence population would be adequate and appropriate until screening tests are available. Thus, until such time as appropriate FDA-licensed, approved, or cleared donor screening tests are available for these disease agents, the required testing would be performed using tests labeled for detection of the organisms.

Under proposed § 1271.80(d), a donor whose specimen tests repeatedly reactive or positive on a test required under proposed § 1271.85 must be determined to be unsuitable. (Repeatedly reactive means initially reactive, then reactive in at least one of two duplicate tests with the same manufacturer's test kit.) Proposed § 1271.80(d)(1)(i) and (d)(1)(ii) set out two exceptions to this general rule. Under the first exception, a repeatedly reactive test for CMV will not make a donor unsuitable unless additional testing shows the presence of an active infection. This exception is being proposed because, although a donor with active CMV poses a risk of CMV transmission, a donor's past infection with the virus does not necessarily present such a risk. The results of CMV testing would accompany the product, under proposed § 1271.55(a)(1)(i), or would be contained in the summary of records that accompanies the product, and should be reviewed by the physician prior to use of the product. The agency believes that the provision of information on CMV status in the materials accompanying the product will be sufficient to allow physicians to make informed decisions about the use of the product in particular patients' circumstances. The agency specifically requests comments on this approach.

The second exception is for a donor whose specimen has tested repeatedly reactive on a non-Treponemal screening test for syphilis and negative on a specific Treponemal confirmatory test. FDA is proposing this exception because it recognizes that non-Treponemal screening tests, which do not test directly for the disease agent, frequently provide false-positive results. Negative results from a Treponemal confirmatory test, which is more specific and, thus, more accurate, will be considered to override an initial false positive.

Blood loss from a potential donor, followed by transfusion or infusion, may result in plasma dilution that affects test results. Plasma dilution is defined in proposed § 1271.3(s) as a decrease in the concentration of the donor's plasma proteins and circulating antigens or antibodies resulting from the transfusion of blood or blood components and/or infusion of fluids. Proposed § 1271.80(d)(2) sets out the requirements for assessing whether a specimen from a donor from whom blood loss has occurred is acceptable. (In the absence of an acceptable specimen, a donor must be determined to be unsuitable.) A specimen taken after blood loss but before the transfusion or infusion is acceptable. In addition, in certain instances an established procedure to calculate dilution (an algorithm) may be used. Proposed § 1271.80(d)(2) is based closely on § 1270.20(h)(2) and (h)(3). FDA discussed the provisions of § 1270.20(h)(2) and (h)(3) in the tissue final rule (see 62 FR 40429 at 40435 through 40436), and the guidance document that accompanied that rule contains information on plasma dilution and algorithms.

2. Specific Requirements (Proposed § 1271.85)

Proposed § 1271.85 sets out specific requirements with respect to donor testing. Proposed § 1271.85(a), (b), and (c) identify the minimum relevant communicable disease agents for which testing is required. Proposed § 1271.85(d) contains retesting requirements for donors of certain reproductive cells or tissues.

The proposed requirements in § 1271.85(a) cover all cells and tissues that are not subject to a regulatory exception from the testing requirement. Under proposed § 1271.85(a), a specimen from a donor of viable or nonviable cells or tissue would be required to be tested for evidence of infection due to: HIV type 1, HIV type 2, HBV, HCV, and *Treponema pallidum*.

In addition to the testing required under proposed § 1271.85(a), a donor of viable, leukocyte-rich cells or tissues would be required under proposed § 1271.85(b) to be tested for evidence of infection due to: HTLV types I and II, and CMV. The agency is proposing to make the distinction between cells and tissues that are rich in leukocytes and those that are not, because the transmission of certain disease agents, such as HTLV types I and II, and CMV, depends on the presence of

viable leukocytes. Stem cells and reproductive cells and tissue, e.g., semen, are examples of leukocyte-rich cells or tissue. In contrast, FDA does not consider corneas, skin, heart valves, dura mater, bone, tendons, ligaments, or cartilage to be leukocyte-rich. The agency specifically requests comments on whether the term “leukocyte-rich” needs additional clarification.

Proposed § 1271.85(c) would require testing for donors of reproductive cells or tissue, in addition to those required by proposed § 1271.85(a) and (b). Proposed § 1271.85(c)(1) identifies *Chlamydia trachomatis* and *Neisseria gonorrhea* as relevant genitourinary disease agents for which testing would be required. However, testing for *Chlamydia trachomatis* and *Neisseria gonorrhea* would not be required if the reproductive cells or tissue are procured by a method that ensures freedom from contamination of the cells or tissue by infectious disease organisms that may be present in the genitourinary tract. FDA is requesting comments and supporting data on whether other genitourinary disease agents should be considered relevant.

Proposed § 1271.85(a), (b), and (c) specify that the purpose of testing is to adequately and appropriately reduce the risk of transmission of relevant communicable diseases. Thus, any test performed under proposed § 1271.85 must be chosen with this purpose in mind. The regulation specifies that testing shall be performed using FDA-licensed, approved, or cleared screening tests in accordance with the manufacturers’ instructions.

The following list represents FDA’s current thinking on the appropriate FDA-licensed, approved, or cleared screening tests that should be used to adequately and appropriately reduce the risk of transmission of relevant communicable disease agents or diseases:

- (1) HIV, type 1: FDA-licensed screening test for anti-HIV–1:
- (2) HIV, type 2: FDA-licensed screening test for anti-HIV–2:
- (3) HBV: FDA-licensed screening test for hepatitis B surface antigen (HBsAg);
- (4) HCV: FDA-licensed screening test for anti-HCV;
- (5) *Treponema pallidum*: FDA-cleared serological test for syphilis;
- (6) Human T-lymphotropic virus, types I and II: FDA-licensed screening test for anti-HTLV I/II; and

(7) Cytomegalovirus: FDA-cleared test for anti-CMV.

In the case of HBV, there are two types of screening test: A test for the surface antigen and a test for the core antibody. Currently, the appropriate test to reduce the possibility of transmission of HBV to a recipient is the surface antigen test because it is a marker of infectivity. Thus, “FDA-licensed screening test for HBsAg” appears on the previous list as an example of a test to be performed for the HBV virus. Testing for the core antibody alone would not accurately evaluate the donor for the possibility of transmission, because the core antibody test could be negative and the donor could still be infectious. Active infection at the time of donation can only be adequately evaluated with the use of the surface antigen screening test, which, if repeatedly reactive, indicates early or chronic HBV infection.

It should be noted that, if the establishment determining the suitability of the donor is aware of any repeatedly reactive screening test for a relevant communicable disease agent that indicates the possible presence of a relevant communicable disease, whether or not the test is the one best suited to adequately and appropriately reduce the risk of disease transmission, then the donor of the cellular or tissue-based product must be determined to be unsuitable under proposed § 1271.80(d)(1). For example, a repeatedly reactive core antibody test for HBV, although not required, would make the donor unsuitable.

Proposed § 1271.80(d) would require retesting of the donor at least 6 months after the date of donation of reproductive cells or tissues that can reliably be stored. Cells or tissues that can reliably be stored are those that maintain function and integrity during storage; some examples include spermatozoa and sperm progenitor cells. The retesting requirement is designed to address the “window period” between the time of infection and the presence of detectable levels of antibodies to communicable diseases and agents such as HCV. Testing would not be complete, and thus a donor-suitability determination could not be made, until the completion of the second round of tests. Under proposed § 1271.60(a), quarantine for these products would last a minimum of 6 months, until completion of testing. For donors of reproductive cells and tissues that can

be reliably stored, FDA considers HBV core antibody screening test to be the most adequate and appropriate retest for HBV.

For all other banked tissue and cells from living donors, FDA recommends but does not propose to require that, where appropriate and feasible, all donors (or mothers of fetal or neonatal donors) be retested 6 months after donation and that the banked cells and tissue be kept in quarantine pending retesting.

3. Dura Mater

CJD, a type of TSE, is a rare, but invariably fatal, degenerative disease of the central nervous system characterized by progressive dementia. Recent reports link the transmission of CJD to recipients of human cadaveric dura mater, particularly allografts manufactured by one company prior to 1987. Thus, FDA proposes to require, in § 1271.85(e), that an assessment be performed for donors of dura mater to detect evidence of TSE.

On March 27, 1997, the World Health Organization (WHO) recommended a ban on the use of human dura mater as an implant because of reports of CJD in a limited number of recipients. Since FDA had established safeguards and guidelines in 1990 to minimize the possibility of such infections, the agency announced on March 31, 1997, that it would not restrict the distribution of FDA-cleared dura mater allografts.

On October 6, 1997, FDA's Transmissible Spongiform Encephalopathy Advisory Committee (TSEAC) discussed the existing safeguards and additional safeguards that needed to be in place to prevent the transmission of CJD by human cadaveric dura mater. The TSEAC's recommendations were transmitted to industry through an FDA letter to manufacturers on March 6, 1998. After comments were received, FDA revisited the issues with TSEAC on April 16, 1998. Based upon the recommendations of the TSEAC at this meeting, the following represent proposed procedures for complying, at the present time, with the testing requirements of proposed § 1271.85(e) and the screening requirements of proposed § 1271.75(a)(4).

After the dura mater has been removed, a full brain autopsy of the donor of dura mater, including gross and histological examination, should be performed by a qualified neuropathologist, to identify evidence of TSE changes. Testing to detect protease-resistant prion protein (PrP-RES) either by immunohistochemistry or Western Blot, is currently a research (investigational use) tool, as there is no FDA-approved or validated test for screening TSE in brain tissue. However, a negative test is considered significant in increasing the level of confidence that the brain and the dura mater are free of TSE. FDA encourages validation of this test. Manufacturers should continue to monitor scientific developments and should incorporate this test if and when it becomes approved for this intended use.

Donors of dura mater should be subject to a consistent screening protocol, including a donor medical history interview that includes questions relevant to TSE risk, as mentioned in the human tissue guidance.

FDA intends to address other recommendations of the TSEAC in future proposed regulations on CGTP's. These include a standard protocol for procuring dura mater, prevention of cross-contamination, use of either a NaOH protocol or other procedure that has been validated to reduce infectivity while preserving clinical utility, archiving of a sample of brain and dura mater tissues, and recordkeeping and tracking requirements.

4. Corneal Tissue

The possibility that corneal tissue may transmit TSE is discussed in section III.D.1 of this document. Although the agency is proposing to require that, for donors of dura mater, an assessment designed to detect evidence of TSE be performed, the recommended method of accomplishing this assessment involves a full brain autopsy, including gross and histological examination, and definitive results are not available for several weeks. At present, this type of testing does not appear feasible for cornea donors, because under present conditions of storage in the United States, corneas must be transplanted within days of procurement in order to maintain their integrity and function. The agency requests comment on the feasibility of testing for TSE in donors of corneal tissue.

F. Exceptions (Proposed § 1271.90)

1. Exceptions From the Requirement for a Donor Suitability Determination

Proposed § 1271.90(a) identifies two situations in which a determination of donor suitability would not be required. In the case of banked cells and tissues for autologous use, cells and tissues are removed from a patient and stored for later use in the same patient. Because the risk of the patient's contracting a new communicable disease from cells or tissues taken from his or her own body is extremely low, FDA is not requiring communicable disease testing or screening. (Any handling and storage requirements for such cells or tissue may be addressed later, in the proposed CGTP regulation.) However, as a general safety measure, FDA recommends that autologous donors be subjected to the same testing and screening as proposed under §§ 1271.75, 1271.85, and 1271.90 for allogeneic donors of comparable human cellular or tissue-based products.

The second situation in which FDA is recommending but not requiring testing is for reproductive cells or tissue donated by a sexually intimate partner of the recipient. In this case, the recipient will likely have been routinely exposed to the donor's semen or other body fluids. Although some screening and testing of the donor and recipient may be appropriate, FDA believes that this should be the responsibility of the attending physician and the donor and the recipient.

2. Labeling Requirements

Although screening and testing would not be required in the two above situations, FDA is proposing certain labeling requirements.

In order to protect those people who may handle the human cellular or tissue-based product, the manufacturer would be required to label a product as "NOT EVALUATED FOR INFECTIOUS SUBSTANCES" unless all donor screening and testing applicable to a comparable human cellular or tissue-based product under proposed §§ 1271.75, 1271.80, and 1271.85 are performed. Thus, if screening and testing results are negative, but not all of the testing and screening that would be required under proposed §§ 1271.75, 1271.80, and 1271.85 are performed, then the product

would be labeled “NOT EVALUATED FOR INFECTIOUS SUBSTANCES.” However, if any screening or testing is performed, and the results indicate the presence of relevant communicable disease agents, or risk factors for and/or clinical evidence of relevant communicable disease, then the product would be labeled with the Biohazard legend shown in proposed § 1271.3(i).

In addition, the manufacturer would be required to label autologous banked cells and tissues as “FOR AUTOLOGOUS USE ONLY.” Such a label would help prevent inadvertent allogeneic administration.

G. Drug and Device Amendments (§§ 210.1, 210.2, 211.1, 820.1)

As discussed in section I of this document, FDA proposes to require that manufacturers of human cellular or tissue-based products regulated as drugs, medical devices, and/or biological products comply with the donor-suitability procedures now being proposed. In a future proposed rulemaking, the agency plans to propose CGTP’s that would be applicable to these products, as well. The donor-suitability and CGTP procedures would be considered part of CGMP requirements for drugs and the Quality System for devices. In order to incorporate these new procedures, FDA is proposing to amend parts 210 and 211 with respect to human cellular and tissue-based products regulated as drugs and/or biological products and part 820 with respect to human cellular and tissue-based products regulated as devices.

FDA proposes to amend § 210.1 by adding new paragraph (c), which would contain the requirement for compliance with the donor-suitability procedures proposed in part 1271 subpart C and the current CGTP procedures to be proposed in part 1271 subpart D as part of the GMP requirements, and which would state that failure to comply with those or other CGMP’s would adulterate the product. (References to the requirements in proposed part 1271 are also proposed to be added to §§ 210.2 and 211.1, to bring those regulations in conformity with the changes in § 210.1.) Comparable amendments are being proposed for § 820.1 to achieve the same result with respect to human cellular and tissue-based products regulated as devices.

IV. Analysis of Economic Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866, under the Regulatory Flexibility Act (5 U.S.C. 601–612), and under the Unfunded Mandates Reform Act (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The Regulatory Flexibility Act requires agencies to analyze whether a rule may have a significant impact on a substantial number of small entities and, if it does, to analyze regulatory options that would minimize the impact. The Unfunded Mandates Reform Act requires that agencies prepare a written statement under section 202(a) of anticipated costs and benefits before proposing any rule that may result in an expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100 million (adjusted annually for inflation in any one year).

The agency believes that this final rule is consistent with the principles identified in Executive Order 12866. OMB has determined that the final rule is a significant regulatory action as defined by the Executive Order and so is subject to review. Because the rule does not impose mandates on State, local, or tribal governments, or the private sector, that will result in an expenditure in any one year of \$100 million or more, FDA is not required to perform a cost-benefit analysis according to the Unfunded Mandates Reform Act.

The Regulatory Flexibility Act requires agencies to prepare a Regulatory Flexibility Analysis for each rule unless the agency certifies that the rule will not have a significant economic impact on a substantial number of small entities. As explained in section IV.C of this document, the agency believes that most of the facilities would not be significantly affected by the proposed rule because they are already performing the infectious disease screening and testing and recordkeeping that is being proposed. However, FDA does not have sufficient data to characterize the size distribution

and other relevant features of small entities involved in reproductive tissue and the impact on these entities is uncertain. FDA has therefore prepared an Initial Regulatory Flexibility Analysis.

A. Objectives and Basis of the Proposed Action

FDA is proposing this action as the next step in the regulation of the rapidly evolving industry of human cellular and tissue-based products. This proposed rule focuses on the first of three general areas of regulation proposed in the approach to cellular and tissue-based products, i.e., preventing unwitting use of contaminated tissues with the potential for transmitting infectious diseases such as AIDS and hepatitis. While acting to increase the safety of the nation's supply of human cellular and tissue-based products, FDA is proposing regulations that would avoid unnecessary requirements. The agency has designed the screening and testing regulations for the specific type and use of each cellular or tissue-based product that would minimize regulatory burden while maintaining safety.

In this rulemaking, the agency is proposing to broaden its regulatory oversight over all human cellular and tissue-based products, including reproductive cells and tissue. This action is focused on the prevention of diseases transmitted by specific cellular or tissue-based products by implantation, transplantation, infusion, or transfer of any cellular or tissue-based product. For example, FDA is now proposing to require cell and tissue donors to be tested for syphilis and screened for TSE. Donors of viable, leukocyte-rich cells or tissue would also be tested for HTLV types I and II, and CMV. Because communicable disease agents can be transmitted by semen and other genitourinary secretions, FDA is proposing to require that donors of reproductive cells and tissue be screened and tested for sexually transmitted diseases. FDA proposes to amend the existing CGMP regulations for drugs and devices to incorporate the screening and testing requirements in proposed part 1271 subpart C. FDA is relying on the authority provided by section 361 of the PHS Act to issue regulations to prevent the spread of communicable disease, as well as its authority under the act to issue CGMP regulations (21 U.S.C. 351(a)(2)(B) and (h) and

360j(f)(1)). FDA has reviewed related Federal rules and has not identified any rules that duplicate, overlap, or conflict with the proposed rule.

B. The Type and Number of Entities Affected

The proposed rule would require manufacturers of human cellular and tissue-based products, including human tissue intended for transplantation, to screen and test donors of cells and tissue used in those products. The rule would require that donors be screened and tested for risk factors for and clinical evidence of relevant communicable disease agents and diseases. The proposed rule would apply to a range of activities conducted at facilities such as tissue banks, blood banks, eye banks, semen banks, infertility treatment facilities, and cord blood banks. However, the number of entities that would be required to comply with this proposal is difficult to ascertain because the agency has not previously regulated certain human cellular and tissue-based products. Although the agency has proposed to require manufacturers of human cellular and tissue-based products to register and list their products and to identify their manufacturer steps, this information will not be available for some time. Consequently, the agency's estimates rely heavily on information obtained from various trade organizations related to the human cellular and tissue-based industry.

As shown in Table 1 of this document, the estimated numbers of facilities affected by the proposed rule are derived from varied industry sources. The Eye Bank Association of America (EBAA) represents about 108 eye banks, which are estimated to be about 95 percent of eye banks in the United States. The American Association of Tissue Banks (AATB) lists approximately 60 accredited tissue banks and projects an additional 40 to 60 members not accredited. As of May 1998, CBER has record of 132 registered blood bank facilities listing "stem cell" as a type of product or establishment. The National Marrow Donor Program (NMDP), which includes establishments that recover peripheral blood stem cells, lists approximately 101 donor centers (these establishments are associated with the American Association of Blood Banks (AABB) or the Foundation for the Accreditation of Hematopoietic Cell Therapy (FAHCT)). Although there is no single national organization that keeps track of the number of facilities for umbilical cord blood

banking, FDA estimates that there are approximately 25 cord blood banks currently operating in the United States. These facilities would also seek accreditation through FAHCT or AABB.

In addition, the proposed rule would apply to facilities involved with reproductive tissue, primarily fertility centers and sperm banks that collect and process donor oocytes or donor sperm. The American Society of Reproductive Medicine (ASRM) has a membership of approximately 300 fertility centers, about 280 of which have provided reports to the 1995 Society for Assisted Reproductive Technology (SART) registry. The ASRM also has a 1996 list of approximately 110 sperm banks operating in the United States. Although ASRM has published guidelines for donor screening and other aspects of oocyte donation, and for therapeutic donor insemination, ASRM does not exercise oversight or provide accreditation of facilities that collect donor tissue or use these tissue products in infertility treatment.

C. Nature of the Impact

The proposed rule includes requirements for donor screening, donor testing, recordkeeping and quarantine of cells and tissue. Donor screening would involve the review of relevant medical records to include a medical history interview (particularly pertaining to communicable disease risk), a current report of a physical assessment for cadaveric donors, and a physical examination for living donors. For living repeat donors, a complete donor-suitability determination procedure would be required at least once every 6 months. The proposed rule would require that a donor specimen be tested for evidence of infection due to relevant communicable disease agents and diseases, with testing conducted within a specified time of recovery of cells or tissue. In general, a donor may be determined suitable if free from risk factors for and clinical evidence of infection due to relevant communicable disease agents and diseases, and if the required testing is negative or nonreactive.

The proposed rule would also require recordkeeping of donor-suitability determinations. Manufacturers would be required to ship human cellular and tissue-based products accompanied by documentation of donor-suitability status, including a copy of the donor's relevant medical

records, results of required testing and the name and address of the establishment that made the suitability determination. The proposed rule requires that establishments that generate records used in donor-suitability determinations retain those records for at least 10 years after the date of the product's use or distribution. The proposed rule would also require that cell and tissue-based products be quarantined until a determination of donor suitability is made, and that products be clearly labeled as under quarantine during that period. The rule would hold manufacturers responsible for the appropriate labeling and documentation of cells or tissue from a donor who is found to be unsuitable.

The extent of the economic impact is expected to be minor for most of these establishments, because the leading industry associations have already established standards for screening that, in most cases, meet or exceed the criteria specified in the proposed rule; and because existing FDA regulations already apply to certain human tissue intended for transplantation (see part 1270). Table 1 of this document lists the types of donor cells and tissue that will be affected by the proposed rule and the associated facilities that collect and bank these tissue products. Table 1 also provides estimates of the number of establishments affected by the proposed rule and the estimated percentage of establishments already in compliance with current industry standards for donor screening and testing. The lists of specific donor screening and testing requirements proposed by FDA can be compared with those currently required by the industry associations.

TABLE 1.—TYPE AND NUMBER OF ESTABLISHMENTS AFFECTED AND PERCENTAGE ALREADY IN COMPLIANCE WITH INDUSTRY STANDARDS FOR DONOR SUITABILITY SCREENING AND TESTING

Type of Human Donor Tissue	Type of Entities Affected (and Estimated Total Number)	Relevant Industry Association Standards Compared to FDA Proposed Regulations	Estimated Percent Entities in Compliance with Industry Standards
Nonreproductive Tissue			
Eye tissue	Eye banks 108 EBAA members (114 total)	21 CFR part 1270 and FDA proposed (s1,s2,s3) ¹ (t1,t2,t3,t5) ² EBAA (s1 through s3) ¹ (t1 through t3) ²	100%
Pericardium, dura mater, heart valves, skin allograft, bone allograft, other viable	Tissue banks 60 AATB members (110 total)	21 CFR part 1270 and FDA proposed (s1 through s3) ¹ (t1,t2,t3,t5) ² AATB (s1 through s3) ¹ (t1 through t5) ²	100%

TABLE 1.—TYPE AND NUMBER OF ESTABLISHMENTS AFFECTED AND PERCENTAGE ALREADY IN COMPLIANCE WITH INDUSTRY STANDARDS FOR DONOR SUITABILITY SCREENING AND TESTING—Continued

Type of Human Donor Tissue	Type of Entities Affected (and Estimated Total Number)	Relevant Industry Association Standards Compared to FDA Proposed Regulations	Estimated Percent Entities in Compliance with Industry Standards
Stem cells; peripheral blood	Marrow donor centers 132 FDA registered facilities donor centers (101 total) collection centers (114 total)	FDA proposed (s1 through s3) ¹ (t1 through t6) ² AABB/FAHCT (s1 through s3) ¹ (t1 through t6) ²	100%
Stem cells; umbilical cord blood	Cord blood banks (25 total)	FDA proposed (s1 through s3) ¹ (t1 through t6) ² AABB/FAHCT (s1 through s3) ¹ (t1 through t6) ²	100%
Reproductive Tissue			
Donor oocyte, embryos	ART facilities & associated labs 281 in 1995 SART report (300 total)	FDA proposed (s1 through s3) ¹ (t1,t2,t3,t5) ² ASRM, CAP (s1) ¹ (t1,t2,t3,t5) ²	Unknown
Donor sperm	Sperm banks 4 in 1996 AATB survey (110 total)	FDA proposed (s1 through s3) ¹ (t1 through t8) ² AATB (s1 through s3) ¹ (t1 through t8) ² ASRM (s1) ¹ (t1,t2,t3,t5,t7,t8) ²	10% Unknown

¹ Screening for: s1: HIV, s2: hepatitis, s3: CJD

² Laboratory Tests: t1: anti-HIV-1-2, t2: anti-HCV, t3: HBsAg, t4: anti-HTLV-1, t5: syphilis, t6: CMV, t7: *Neisseria gonorrhea*, t8: *Chlamydia trachomatis*

Based on communications with representatives of several industry associations and facility managers, FDA estimates that the number of facilities currently in compliance with industry standards for donor screening and testing approaches 100 percent for several affected types of tissue product. Facilities handling reproductive tissue are the primary exception to this finding, and also represent the greatest area of uncertainty for this analysis. There is currently no single reliable source of information on fertility center or sperm bank compliance with AATB standards or ASRM guidelines. A small percentage of sperm banks are members of the AATB and are known to comply with that organization's requirements for screening and testing, but little is known about the standards for screening used at other facilities. Because this information is essential for the estimation of economic impact, FDA requests detailed industry comment on current donor screening and testing practices in these facilities.

In addition to the proposed donor screening and testing, the proposed rule is expected to require facility staff time to align current quarantine, sample labeling and recordkeeping systems with the requirements of the proposed rule. As shown in Table 2 of this document, all of the industry associations already specify requirements for these procedures. With the exception of facilities handling reproductive tissue, the current industry standards adopted by most facilities are at least as stringent as those included in the proposed rule.

TABLE 2.—CORRESPONDENCE OF FDA-PROPOSED REQUIREMENTS TO CURRENT INDUSTRY STANDARDS FOR SPECIMEN QUARANTINE, LABELING, AND RECORDKEEPING

FDA-Proposed	AATB Current	EBAA Current	AABB Current	FAHCT Current	ASRM Current
Quarantine	X ¹	X ¹	X ¹	X ¹	Donor sperm; not oocyte
Labeling	X ¹	X ¹	X ¹	X ¹	X ¹
Record Retention	X ¹	X ¹	X ¹	X ¹	Recommended; not required

¹ "X" means corresponds.

Due to the disparity in the amount of available information and the potential impact of the rule on nonreproductive versus reproductive tissue establishments, these two broad categories of tissue establishments are treated separately in the impact analysis that follows.

1. Impact on Nonreproductive Tissue Establishments

(a) *Impact of donor screening and testing.* As summarized in Table 1 of this document, most nonreproductive tissue establishments are already in compliance with the proposed FDA donor screening and testing requirements, as a result of following their own industry association standards and FDA current regulations. The cost of compliance with these provisions will be minimal for these establishments.

(b) *Impact of recordkeeping and tissue quarantine.* The burden of recordkeeping and tissue quarantine requirements will reflect the staff time needed to compare current recordkeeping and facility procedures with those required by the proposed standard and to make modifications where needed in current facility procedures. Such changes are expected to be minor for most nonreproductive tissue establishments.

FDA estimates that it would take approximately 8 to 40 hours to compare the proposed regulations against a facility's current standards. This process would be performed by a staff person who acts as a regulatory reviewer, a supervisor, or a manager of quality assurance. Assuming a labor cost of \$40 per hour, this standards reconciliation effort would result in a one-time cost per facility ranging from \$320 to \$1,600. Applying this range of cost per facility to the approximately 380 nonreproductive tissue facilities yields a potential impact that ranges from \$121,600 to \$608,000.

2. Impact on Reproductive Tissue Establishments

(a) *Impact of donor screening and testing.* As indicated in Table 1 of this document, the current rate of compliance with industry standards is unknown among reproductive tissue establishments. Thus, FDA cannot develop a precise estimate of regulatory costs. As an upper bound figure, however, FDA assumed that 100 percent of facilities involved with oocyte donation and 80 percent of sperm banks would need additional screening and testing. Although the out-of-compliance sperm banks constitute a majority of the firms in that industry, they are primarily small operations that are estimated to serve only 5 percent of all sperm donors.

(i) *Oocyte Donor Screening and Testing.* The estimated impact of the proposed rule on establishments involved in oocyte donation is based on 1995 data reported by SART, an organization of assisted reproductive technology providers affiliated with ASRM. Approximately 70 percent of ART centers reporting in 1995 had performed at least one cycle of ART with donor eggs. In 1995, donor eggs were used in approximately 8 percent of all 59,800 ART cycles, or 4,783 cycles. (Although 78 percent of those cycles used fresh embryos, the proposed quarantine rules would likely necessitate the use of frozen embryos in all donor cycles, with some potential associated reduction in the success rate per donor in vitro fertilization (IVF) cycle (Ref. 1). FDA believes that all infertility treatment centers already conduct medical exams and history-taking and perform some laboratory testing prior to egg retrieval for any potential oocyte donor. Compliance

with the proposed standard, however, may entail adding some additional blood testing and screening questions to the interview.

The cost of additional blood work (including HIV 1-2, hepatitis B, hepatitis C, and syphilis) is estimated at about \$123 per donor (Ref. 2). The additional time to interview and record information in donor screening is estimated to cost about \$37, based on the assumption that approximately half of the required screening is already being done, and the estimated cost of a full health history interview is \$75 ($\$37 \sim \$75/2$) (Ref. 3). Thus, the additional cost per donation is estimated at \$160 ($\$123 + \37). Based on a reported cost of \$11,868 (Ref. 4) per donor oocyte cycle, this cost translates to a 1.3 percent increase ($(\$160 + \$11,868)/\$11,868$) in the cost of therapy per cycle.

The cost of screening egg donors will depend on the number of donor cycles attributable to each screened donor. If each donor contributes eggs for only one cycle, and the rejection rate is low (assumed to be 0.57 percent, which is the estimated prevalence rate of HBSAG positivity among parturient women) (Ref. 5), the number of donors to be tested would be 4,810 ($4783/(1 - 0.0057)$). If each donor contributes eggs for two donor cycles, the number of donors to be screened would be 2,405. These alternative assumptions imply a total cost to U.S. facilities involved in oocyte donation of from \$386,000 to \$772,000 per year, as shown in Table 3 of this document.

TABLE 3.—ALTERNATIVE OOCYTE DONATION SCENARIOS AND ASSOCIATED DONOR SCREENING COSTS

Screen/Test Cost Per Donor $\$123.40 + \$37.00 = \$160.40$	2 ART Cycles Per Donor = 2,405 $\$386,000 (\$160.40 \times 2,405 = \$385,762)$	1 ART Cycle Per Donor = 4,810 Donors $\$772,000 (\$160.40 \times 4,810 = \$771,524)$
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(ii) *Sperm donor screening and testing.* The agency has conducted an extensive search for current information on the extent of infectious disease screening for sperm donors, but has found little current information available. The Congressional Office of Technology Assessment (OTA) conducted a survey of establishments involved in sperm donation in 1987, and found that all commercial banks surveyed performed routine screening and testing for HIV, but only 45 percent of private physicians included this screening. The most recently available data includes a list of approximately 110 commercial sperm banks developed by ASRM in 1996, and a 1996 registration

survey of the AATB that includes data for 4 sperm banks. The agency is aware that some sperm banks that have applied, but are not yet accredited members of AATB, are nonetheless following AATB standards. It is also likely that some other facilities have informally adopted AATB standards. This analysis assumes that all sperm banks currently perform HIV screening and testing, as reported by OTA in 1987, and a smaller percentage of facilities additionally follow all AATB screening and testing standards.

Based on recent conversations with sperm banking industry experts, FDA estimates that the largest 20 sperm banks account for approximately 95 percent of the commercial production of donor sperm, and that these facilities are compliant with AATB standards for donor screening and testing. The agency analysis therefore assumes that the 20 largest facilities, which account for most industry production, will experience minimal impact; while the remaining 90 facilities, which have extremely small volumes of production, will be more significantly affected. The very small sperm banks are described by an industry expert as typically functioning within a physician office practice (e.g., that of an obstetrician or gynecologist). The sperm banking in these facilities is generally offered as an additional service to patients receiving fertility treatment, and is not the primary line of business within these establishments.

The total estimated cost of the proposed screening and testing procedures for sperm banking facilities is based on the number of sperm donors who would require screening and testing, and their respective unit costs. Due to the lack of data on the actual number of sperm donors, the agency estimated the number based on projected therapeutic donor insemination TDI demand. The level of TDI demand has likely changed over time, with advances in treatment for male factor infertility. For example, the development of intracytoplasmic sperm injection ISCI used in conjunction with in vitro fertilization has enabled some couples to forego TDI in favor of ISCI using the male partner's sperm (Ref. 6). In 1985, an estimated 70,000 women per year received TDI (Ref. 7), compared to an estimated 171,000 women who reported ever receiving artificial insemination with donor sperm, in the National Survey of Family Growth (NSFG) conducted in

1995. If the NSFG respondents referred only to experience over the past 5 years, this would translate to approximately 34,200 women receiving TDI per year. Assuming an average of three cycles of therapy per patient per year, these data yield an estimated demand for TDI donor units of approximately 102,600 units per year. This figure is consistent with an industry expert estimate of current U.S. TDI production of 100,000 units per year.

Clinical literature indicates that most sperm donor attrition occurs prior to the blood testing stage of donor screening. For example, in one study of donor recruitment in which the clinic followed AATB and ASRM standards, of the total of 199 potential donors initially recruited, 174 were rejected; 172 of whom were rejected before blood testing, with only 2 (1 percent) rejected based on the blood test results (Ref. 8). Based on these findings, the agency assumes that the number of donors who will require infectious disease testing is approximately equal to the number of donors needed to supply the level of demand for TDI. Thus, FDA's estimate is based on the previous TDI unit demand combined with the maximum number of births per donor suggested in ASRM guidelines (Ref. 9), the average delivery rate per cycle of intrauterine insemination, an assumed 10 donated specimens per donor per year, and 4 donation units per donor specimen (Ref. 10). These factors yield an estimated 2,565 donors required per year. Assuming that the number of donors already screened and tested is proportionate to the volume of production accounted for by facilities compliant with AATB standards, FDA estimates that approximately 5 percent of all donors ($0.05 \times 2,565 = 128$), or 128 donors per year, may need to be newly screened and tested to meet the requirements of the proposed rule.

The screening cost per donor is assumed to include an initial medical history and physical, a 6-month followup exam, and an abbreviated screening at the time of each donation. Based on rates published on the Internet (Ref. 3), the agency estimates that a full medical exam may cost \$175, a less extensive followup exam will cost approximately \$75 (a published fee for a health history review), and the abbreviated screening at the time of each donation will cost approximately

\$15 (i.e., one-fifth of the time required for a full history review). One repeat donor visit per year is assumed. Thus, the total cost of this screening is estimated to be \$265 per year per donor.

The lab tests for prospective donors include those listed in Table 1 of this document, with 6-month followup blood tests for hepatitis B and C, HTLV-1, and syphilis. The cost of additional testing, based on screening test fees published on the Internet (Ref. 2), is \$230.16 for initial complete blood testing, plus \$123.40 for followup blood testing after a 6-month quarantine period, plus \$113.30 for bacterial testing. The total cost of the additional lab work is estimated to be \$467 per donor per year ($\$230.16 + \$123.40 + \$113.30 = \466.86). Because these estimates are based on charges to facility clients, they are likely to represent an upper bound on actual facility costs. Using these figures, the estimated total industry cost per year is approximately \$94,000 ($128 \times (\$265 + \$467) = \$93,696$).

(b) *Impact of donor recordkeeping and tissue quarantine.* The impact of recordkeeping and tissue quarantine for reproductive tissue establishments will reflect the staff time required for: (1) A one-time review and modification of current recordkeeping and facility procedures to bring them into alignment with the proposed standard, and (2) on-going, expanded practices for each donor who undergoes screening and testing to meet the requirements of the proposed rule.

FDA estimates that the one-time review and alignment of current facility procedures will require approximately 8 to 40 hours at each facility. As with nonreproductive tissue facilities, this process would be performed by a regulatory affairs analyst, a supervisor, or a manager of quality assurance. Assuming a labor cost of \$40 per hour, this standards reconciliation effort would result in a one-time cost per facility ranging from \$320 to \$1,600. This estimate corresponds to a total one-time cost for all reproductive tissue facilities that ranges from \$131,200 ($\$320 \times (300 + 110)$) to \$656,000 ($\$1,600 \times (300 + 110)$).

The recurring requirements for tissue quarantine, labeling, recordkeeping and record retention at reproductive tissue facilities are based on the estimated staff time needed to create and retain records of medical history, screening information, and lab testing for each prospective donor from

whom specimens are collected. The records must comply with the information requirements of the proposed rule and are estimated to require approximately 4 hours per donor per year of clerical staff time, with an assumed labor cost of \$24 per hour for clerical staff (\$96 per donor per year). Table 4 of this document summarizes the potential range of recurring costs for all reproductive tissue facilities. As shown, the estimated costs range from \$243,000 to \$474,000, depending on the assumed number of donors.

TABLE 4.—RANGE OF RECURRING COSTS FOR REPRODUCTIVE TISSUE

128 sperm donors 1 cycle per egg donor	\$243,000 $((128 + 2,405) \times \$96 = \$243,168)$
128 sperm donors 2 cycles per egg donor	\$474,000 $((128 + 4,810) \times \$96 = \$474,048)$

The size and range of these estimates reflects the agency's current lack of information about typical donor practices for reproductive tissue. If a higher rate of donation per donor is typically achieved by facilities, compared to that assumed in this analysis, the additional cost burden may be much lower than these estimates would indicate. More generally, if the current level of facility donor screening and recordkeeping is more stringent among reproductive tissue facilities than assumed in this analysis, the overall cost of compliance with the proposed rule will be lower than these preliminary estimates suggest.

Uncertainty about current practice and the level of compliance results in range estimates of the cost impact of the proposed rule. However, because most industry sectors already follow industry standards requiring donor testing and screening, the overall impact is expected to be small. Table 5 of this document provides a summary of the impacts across the different industry sectors included in the analysis. The total annualized cost for the 380 nonreproductive tissue facilities is estimated to range from \$17,000 to \$87,000, reflecting agency uncertainty about the extent of effort devoted to one-time review and alignment of existing standard operating procedures with the proposed donor screening rule provisions. This translates to an average cost of \$45 to \$229 per facility.

The annualized cost of compliance for the ART industry ranges from approximately \$631,000 to \$1.302 million, reflecting current uncertainty about the number of oocyte donors and the number of donations per donor per year. These costs translate to an average cost of approximately \$2,103 ($\$631,000/300$) to \$4,340 ($\$1,302,000/300$) per facility per year. In general, assumed higher rates of donation per year, or a lower number of total donor oocyte cycles per year, will result in lower industry costs. By the same token, lower rates of donation per donor, or higher total donor cycles performed per year, will result in higher donor screening costs.

The total annualized cost impact on the sperm banking industry is based on an estimated TDI demand of approximately 102 thousand units per year, and assumed current compliance of the top 20 commercial banks, which account for approximately 95 percent of industry production. The total annualized costs range from approximately \$111,000 to \$131,000. These industry totals yield an average annualized cost range of \$1,234 ($\$111,000/(110-20)$) to \$1,456 ($\$131,000/(110-20)$) per facility estimated to be noncompliant with the proposed standard.

TABLE 5.—DONOR SUITABILITY COST ANALYSIS SUMMARY TABLE¹

Type of Facility	Total One-time Cost	Total Recurring Cost	Total Annualized Cost ²
Nonreproductive Tissue—Eye Tissue, Conventional Tissue, and Stem Cell			
(a) Donor screening and testing	Minimal	Minimal	Minimal
(b) Recordkeeping and tissue quarantine	\$121,600 to \$608,000	Minimal	\$17,000 to \$87,000
Reproductive Tissue—ART Facilities			
(a) Donor screening and testing	Minimal	\$386,000 to \$772,000	\$386,000 to \$772,000
(b) Recordkeeping and tissue quarantine	\$96,000 to \$480,000	\$231,000 to \$462,000	\$245,000 to \$530,000
<i>ART subtotal</i>	\$96,000 to \$480,000	\$617,000 to \$1,234,000	\$631,000 to \$1,302,000
Reproductive Tissue—Sperm Banks			
(a) Donor screening and testing	Minimal	\$94,000	\$94,000
(b) Recordkeeping and tissue quarantine	\$35,200 to \$176,000	\$12,000	\$17,000 to \$37,000
<i>Sperm subtotal</i>	\$35,200 to \$176,000	\$106,000	\$111,000 to \$131,000
Total Tissue Industry			
Total	\$252,800 to \$1,264,000	\$723,000 to \$1,340,000	\$759,000 to \$1,520,000

¹ Rounded to the nearest thousand² At 7% interest rate over 10 years

D. Estimated Benefits of Proposed Rule

The proposed action would provide oversight for the full spectrum of human cellular and tissue-based products that are now marketed and may be marketed in the future. This action is intended to improve protection of the public health and increase public confidence in new technologies, while permitting significant innovation and imposing minimal regulatory burden. An important benefit of the rule will be the establishment of a consistent standard of safety to help ensure equivalent protection from transmissible diseases for all recipients of therapy involving cellular and tissue-based products, regardless of the health condition for which they are being treated. The proposed rule would help minimize risk to all patients of exposure to several life-threatening, in some cases incurable, diseases including HIV, HBV, HCV, CJD and others. These risks would be minimized through validated screening procedures, lab tests, and adequate labeling to avoid unwitting use of unsafe specimens. Each of the infectious diseases screened (see Table 1 of this document) will provide added patient safety protection and public health benefit.

The risks of disease transmission vary by type of cellular and tissue-based product. Donor screening, testing, and other measures to reduce the risks of transmission for various types of tissue will correspondingly yield a different relative reduction in disease risk. For example, expansion of blood donor screening and improved laboratory tests have dramatically reduced the risk of blood transfusion-transmitted disease. The risk of HIV infection has dropped from a reported 1 in 100 units in some U.S. cities to approximately 1 in 680,000 units. The risk of transmission of HBV has been reduced from 1 in 2,100 to 1 in 63,000 units, and the transmission risk for HCV has been lowered from 1 in 200 units in the early 1980's to the current level of 1 in 100,000 units (Ref. 11). These levels of risk reduction based on blood donors, offer an illustration of the kind of improvements in safety that might be achieved through improved and expanded screening of donors.

As described earlier, most nonreproductive tissue establishments are assumed to be already compliant with the proposed rule and therefore have already achieved the level of intended risk

reduction. The discussion of benefits resulting from the proposed rule will therefore focus on some key areas of risk and potential benefit of the proposed requirements for reproductive tissue recipients. The discussion that follows will consider the risks of sexual transmission of disease that will be reduced through expanded screening among reproductive tissue donors, focusing on the reduced risk of two life-threatening chronic diseases that can be transmitted through donor tissue: HBV and HCV.

The expansion of screening among reproductive tissue donors is expected to produce important reductions in disease risk, as evidenced by the apparent reductions in HIV risk that have already been achieved through screening. The risk of HIV transmission through TDI appears to be much lower since screening for HIV was recommended by the Center for Disease Control and Prevention (CDC) in 1985. A total of six documented and two possible cases have been reported to the CDC as of December 1996 (Ref. 7).

The risks of transmitting HBV and HCV through reproductive tissue should be substantially reduced as a result of donor screening, based on the significance of self-reported risk factors as predictors of the findings of blood screening for HBV and HCV (Ref. 12). Compared to HCV, HBV presents a higher risk of sexual transmission. In 1991, heterosexual activity is reported to account for 41 percent of all cases of HBV (Ref. 13). HBV transmission has also been reported by use of TDI; in 1982 a physician used semen from an unscreened donor (later found to carry HBsAg) to inseminate several women, one of whom later developed HBV (Ref. 14).

HBV-infected mothers can transmit the disease to their infants. Forty-two percent of infants born to women with HBsAg positivity (adjusted for HBeAg status) are at risk of HBV infection, and an additional 30 percent of infants born to HBsAg-positive mothers become infected between 1 and 5 years of age. Prospective studies of infected infants or young children, indicate that 25 percent will die from primary hepatocellular carcinoma (PHC) or cirrhosis as adults. The lifetime medical cost per case of PHC and cirrhosis is estimated to be \$96,500 (Ref. 15). An analysis of the cost-effectiveness of prenatal screening and testing of mothers, with vaccination for positive

screens, estimates that such screening and intervention would prevent 69 percent of the chronic HBV infections acquired perinatally or later in life (Ref. 16). This rate of effectiveness may provide an indication of the potential benefit of HBV screening in the proposed rule.

The risk of sexual transmission is estimated to be lower for HCV, compared to HBV. The CDC estimates the rate of transmission from female to male partners, and the rate of transmission from mother to child, to each be approximately 5 percent. However, there is no vaccine intervention available for HCV, although interferon-alpha therapy has been found effective in eliminating the virus for at least some patients and drug combinations (e.g., Interferon and Ribovirus) may be even more effective. Although most patients infected with HCV are relatively healthy during most of their lives, an estimated 30 percent of those infected will eventually die of liver-related causes; an estimated 8,000 patients per year (Ref. 15). The average cost of care per year for persons with liver disease from chronic HCV is estimated to range from \$24,600 for patients without interferon-alpha therapy to \$26,500 per year for those receiving a 12-month course of therapy. The latter is estimated to provide patients with an additional 0.37 quality-adjusted life-years (Ref. 16).

Screening third-party tissue donors is expected to significantly reduce the excess morbidity and mortality caused by hepatitis B and C. As noted earlier, there are an estimated 2,405 to 4,810 oocyte donors and 2,565 sperm donors per year. If these populations experience recently reported prevalence rates for HVC (9.8 percent) and HBV (27.6 percent) (Ref. 12), then screening for significant risk factors and disease markers will result in reduced HBV and HCV exposures for the patient population at risk. The population at risk each year is estimated to include 1,600 to 4,700 women undergoing IVF with donor eggs, and 1,300 newborns delivered as a result of this

therapy¹; and 34,200 to 70,000 women receiving TDI, and 8,800 newborns delivered as a result of that therapy.

E. Initial Regulatory Flexibility Analysis

FDA's objectives and authority for issuing the proposed rule are described in section II of this document. Based on its initial analysis, FDA finds that a substantial number of the establishments required to comply with this proposed rule may be small business entities, particularly facilities involved with reproductive tissue products. The Small Business Administration defines a small business in this SIC industry sector to be an establishment with \$5 million or less in annual receipts (Ref. 17). The economic impact analysis presented in section IV.C of this document includes estimates of the number of entities to which the proposed rule will apply. Each set of facilities involved in the tissue banking sectors includes some facilities that would be classified as small business entities.

A 1995 study of conventional tissue banks (Ref. 18) reports average annual revenues of \$1.23 million per facility. Most nonreproductive tissue facilities are assumed to have a comparable level of average revenues. Reproductive tissue experts estimate that 65 percent of ART facilities have average revenues of approximately \$2.5 million per year and the remaining 35 percent have average revenues of \$11.5 million per year. Industry experts also estimate that 19 of the 20 largest sperm banks have average annual revenues of approximately \$2 million per year, and 1 of the 20 largest facilities has annual revenues greater than \$5 million. Thus, the majority of tissue facilities are small entities. Nevertheless, as noted in the preceding cost analysis, most of these facilities would not be significantly impacted by the proposed rule, because they are already performing the proposed infectious disease screening and recordkeeping.

¹ The range of 1,600 to 4,700 IVF patients is based on a reported 4,783 cycles of IVF with donor egg reported

for 1995, and the assumed number of cycles of therapy per patient. The number of newborns is based on an

Table 6 of this document presents estimates of the average cost per facility as a percentage of average annual revenues. In addition to facility revenues Table 6 presents the estimated annual practice income for Ob/Gyn practices, because some operate a small donor sperm bank as an additional service to patients, but may not currently comply with the screening and testing requirements of the proposed rule. The estimated annual revenue of \$252,000 per year for individual physician practices is based on the mean physician income of \$215,000 after expenses and before taxes for the Ob/Gyn specialty category reported in the 1992 American Medical Association survey (Ref. 19), adjusted to 1998 assuming an average annual wage inflation of 2.7 percent, based on yearly rates reported by the Bureau of Labor Statistics.

TABLE 6.—ESTIMATED ANNUALIZED COST PER FACILITY AS A PERCENTAGE OF ESTIMATED ANNUAL REVENUE

Number of Facilities That May Be Classified as Small Entities	Average Annualized Cost per Facility	Average Annual Revenue per Facility	Annualized Cost as Percentage of Annual Revenue
Nonreproductive Tissue—Eye Tissue, Conventional Tissue and Stem Cell			
380-all potentially small	\$45 to \$229	\$1.2 million	0.004 to 0.019%
Reproductive Tissue—ART Facilities			
195 (65% of 300 facilities)	\$2,103 to \$4,340	\$2.5 million	0.08 to 0.17%
Reproductive Tissue—Sperm Banks			
19-larger commercial banks	\$1,234 to \$1,456	\$2.0 million	0.06 to 0.08%
90-physician practice-based banks	\$1,234 to \$1,456	\$252,000	0.5 to 0.6%

As noted in Table 6 of this document, the greatest cost will be incurred by facilities involved with reproductive tissue. Nevertheless, the estimated impact on most small facilities does not appear to be significant. The expected increase in cost per facility ranges up to 0.6 percent of annual revenues. However, if current practices actually involve a much lower level of infectious disease screening than assumed in this analysis, the impact of the proposed screening and testing requirements would be higher than expected. Because accurate information on current industry practices is essential for a valid assessment of economic impact, FDA requests detailed industry comment on its estimate of the number of affected small facilities and their current donor screening, testing, tissue quarantine, and recordkeeping practices.

Although the proposed rule would impose some costs on small entities involved in the manufacture of cellular and tissue-based products, the agency believes that the proposed approach

represents an effective means of protecting patient safety and public health in the collection of donor cells and tissue for manufacture. The less burdensome alternatives to the proposed approach involve fewer requirements for small entities (the vast majority of facilities in this industry), but fail to provide fundamental aspects of product safety. For example, reliance on published FDA guidance for donor suitability screening and testing, rather than establishing a regulatory requirement, would provide the agency with no basis for ensuring compliance. Thus, agency guidance may have no greater influence than current industry voluntary standards, which have similar provisions, but have failed to persuade all facilities to adopt comprehensive screening and testing practices. FDA's guidance, alone, therefore, would not be expected to provide adequate public protection from the safety risks associated with infected donor-derived products.

Another alternative would involve the waiving of some of the donor screening and testing requirements for small facilities. However, as noted previously, nearly all facilities in this industry are small. Moreover, this alternative would increase tissue product safety risks, if small facilities that currently screen and test donors on a voluntary basis choose to discontinue this practice due to an FDA-granted waiver. For example, waiving a requirement for donor screening would eliminate an extremely cost-effective first-tier level of safety protection because prospective donors deferred or disqualified at this stage need not undergo further testing. Similarly, waiving the proposed requirements for blood testing would expose patients, as well as tissue facility and medical staff, to avoidable risks of infectious disease that may be undocumented in a patient's medical history, or be unknown to, or not mentioned by the living donor or donor family during screening.

A waiver of the requirements for tissue quarantine to allow for the window period of donor infectivity prior to detection through blood tests would expose product recipients and the public to risks of infectious disease agents that cannot be immediately detected through most currently available blood tests (e.g., tests for HIV and HCV). Recordkeeping for donor screening and testing is also critical to product recipient and public safety. Adequate documentation and record retention

ensure that cellular and tissue-based products can be tracked to their source in the event of infection or other adverse reactions that result from donor tissue characteristics.

In summary, the agency believes that abridged requirements for donor screening and testing, based on voluntary standards or facility size criteria, would provide inadequate protection against the risk of infectious disease. Most notably, the absence of regulation allows reproductive tissue facilities to omit the proposed screening and testing of tissue donors that is routinely completed for other cellular and tissue-based products, thus exposing infertility patients to a disproportionate risk of several life-threatening infectious disease agents.

To alleviate the impact on small entities while continuing to protect public health, the agency is proposing to recommend, but not require, that manufacturers follow screening and testing procedures for relevant communicable disease agents and diseases when a cellular or tissue-based product is used in the same person from whom it is obtained, or in a sexually intimate partner of a reproductive-tissue donor. A recommendation is considered adequate in this instance because the risk of disease transmission from such activities is believed minimal.

Under the proposed rule, small entities involved with reproductive tissue will be required to meet the same safety and quality standards as large reproductive tissue facilities and other cellular and tissue-based product manufacturers, regardless of size. The specific requirements for donor screening and testing, the required recordkeeping, and the required types of professional skills are described in the economic analysis provided previously. This analysis includes an accounting of all major cost factors, with the exception of the reduced potential liability currently encountered by those reproductive tissue facilities that fail to provide the level of protection from infectious disease that is considered a standard of good practice in other sectors of the tissue-based product industry. The relevant Federal rules that are related to the proposed rule are discussed in section II of this document. This economic analysis provides a summary of the private industry standards that overlap the proposed Federal standard, but as discussed, there is no current regulation of reproductive tissue that would duplicate the proposed rule. Consequently, FDA finds that the

proposed regulation would enhance both public health and public confidence in the safety and utility of transplanted cells and tissues, while imposing only a minimum burden on the affected industry sectors.

V. The Paperwork Reduction Act of 1995

This proposed rule contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 3501–3520). A description of these provisions is shown as follows with an estimate of the annual reporting and recordkeeping burden. Included in the estimate is the time for reviewing the instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

FDA invites comments on: (1) Whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: Documentation and Reporting of Suitability Determination for Donors of Human Cellular and Tissue-based Products.

Description: Under the authority of section 361 of the PHS Act, FDA is proposing new regulations to require manufacturers of human cellular and tissue-based products to screen and test the donors of cells and tissues used in those products for risk factors for and clinical evidence of relevant communicable disease agents and diseases. FDA is proposing that donor suitability determination regulations apply to all establishments covered by the proposed registration rule. The determination of whether a donor is suitable or unsuitable would be made by a responsible person and would be based on the results of required donor screening and testing. Manufacturers

would be required to ship a human cellular or tissue-based product accompanied by documentation of the donor suitability determination. This requirement would apply to a human cellular or tissue-based product from a donor determined to be suitable as well as to a product from a donor determined to be unsuitable and made available for use under certain provisions. The accompanying documentation would contain a copy of the donor's relevant medical records, results of testing, the name and address of the establishment that made the donor suitability determination, and a statement whether, based on the results of the screening and testing of the donor, the donor has been determined to be suitable or unsuitable. With the use of a product from an unsuitable or incompletely tested donor, documentation by the manufacturer would be required showing that the recipient's physician was notified of the screening and testing results, the physician authorized the use of the product after determining there is an urgent medical need, the recipient or the recipient's legal representative was informed of the communicable disease risk, and the recipient or the recipient's legal representative consented to use of the product.

The agency proposes to require that records be retained at least 10 years instead of the current 5 years. This increase in retention time is necessary because certain cellular and tissue-based products have storage periods longer than 5 years. In addition, advances in medical technology have created opportunities for diagnosis and therapy for up to 10 years after recipient exposure to a donor later determined to be at risk for communicable disease agents or diseases.

These proposed provisions are intended as safeguards to prevent the transmission of communicable diseases that may occur with the use of cells and tissues from infected donors. Through this action FDA will improve its ability to protect the public health by controlling the spread of communicable disease.

Description of Respondents: Manufacturers of cellular and tissue-based products.

Based upon recent information from trade organizations related to the manufacturing of products utilizing cells and tissues and the agency's experience, FDA has estimated the following burden for each provision that describes a collection of information.

In the proposed registration rule, the agency proposed § 1271.10 and estimated the burden of collection of information under that provision. In this proposed rule, the agency is modifying proposed § 1271.10. Consequently, a revised estimate for the reporting burden is provided as follows. Although the modifications to proposed § 1271.10 do not effect the original burden estimates, new information from trade associations supports an increase in the estimate of affected manufacturers from 680 to 806. Under proposed § 1271.10 each manufacturer would be required to update its product listings twice a year. For each update, the agency estimates approximately 0.75 hours to complete.

Under proposed § 1271.55(a), approximately 857 manufacturers (224 manufacturers of conventional and eye tissue, 157 manufacturers of peripheral and cord blood stem cell products, 410 manufacturers of reproductive tissue, and 66 manufacturers of products regulated under the act and/or section 351 of the PHS Act) would be required to provide a summary of records. An estimated total of 523,231 cells and tissues (approximately 309,000 conventional tissue products, 86,000 eye tissue products, 6,031 stem cell products, and 122,200 reproductive cells and tissue products) are manufactured into products per year. The agency estimates that for each product, a manufacturer will expend approximately 0.5 hours to prepare the summary of records. Manufacturers of conventional and eye tissue are currently required to provide a summary of records under § 1270.33(d), which proposed § 1271.55(a) would replace.

Under proposed § 1271.65(c)(2), when a cellular or tissue-based product is used prior to completion of screening and testing due to an urgent medical need, a manufacturer would provide a list of the completed and incomplete results with the product. This would be a new practice for 731 manufacturers. Out of 791 manufacturers who could be affected by this provision, approximately 60 manufacturers follow this procedure as usual and customary practice under AATB standards and would not be affected by this proposed section. The agency believes that the use of a product from an unsuitable or incompletely tested donor when there is an urgent medical

need may occur approximately once a year and that each listing should result in approximately 0.25 hours to complete.

Under proposed § 1271.50(b), documentation of donor suitability would be required for the first time for approximately 410 manufacturers. Out of a total of 791 manufacturers of cellular and tissue-based products, there would be no added burden for approximately 381 manufacturers who document donor suitability as usual and customary practice under the trade organization standards. In table 5 of this document, FDA estimates that § 1271.50(b) would impose a new collection of information requirement on 410 manufacturers of reproductive cellular and tissue-based products, each of which would document the suitability of an estimated 11 donors per year, or 4,640 donors, expending approximately 5 hours per document for a total of 55 hours per manufacturer per year.

Under proposed § 1271.55(b), manufacturers would be required to retain records for 10 years. The requirement would affect 410 manufacturers of reproductive cells and tissues. Three hundred and eighty-one of a total 791 manufacturers already retain records for a minimum of 10 years as usual and customary practice under trade organization standards. FDA estimates 0.5 hours per manufacturer to annually retain records. This estimate reflects an average of time that would be necessary to create records for retention from advanced methods of recordkeeping, such as electronic formatting which can improve the ability of manufacturers to more easily retain and retrieve records, to copying records onto microfiche.

Under proposed §§ 1271.65(b)(3) and (c)(3), when a product that is unsuitable or not fully screened or tested is used, approximately 791 manufacturers of cellular and tissue-based products would be required to document notice of the results of testing and screening to the physician, the authorization from the physician after determining there is an urgent medical need, the agreement from the physician to explain the risk to the recipient, and to obtain consent from the recipient before using the product. The agency estimates that such documentation would occur

approximately once annually per manufacturer and that each manufacturer would expend approximately 2.0 hours to create such document.

TABLE 7.—ESTIMATED ANNUAL REPORTING BURDEN¹

21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
1271.10	806	2	1,612	0.75	1,209
1271.55(a)	857	610.5	523,231	0.5	261,615.5
1271.65(c)(2)	731	1	731	0.25	183
Total					263,007.5

¹ There are no capital costs or operating and maintenance costs associated with this collection of information.

TABLE 8.—ESTIMATED ANNUAL RECORDKEEPING BURDEN¹

21 CFR Section	No. of Recordkeepers	Annual Frequency per Recordkeeping	Total Annual Records	Hours per Recordkeeper	Total Hours
1271.50(b)	410	11	4,640	55	22,550
1271.55(b)	410	11	4,640	5.5	2,255
1271.65(b)(3) and (c)(3)	791	1	791	0.5	395.5
Total					25,200.5

¹ There are no capital costs or operating and maintenance costs associated with this collection of information.

The agency estimates that there will be no new or significant increase in maintenance costs for the maintenance of records for the proposed 10-year period instead of the current 5-year retention period, because modern storage technology has markedly reduced the space needed to store records.

Under section 1320.3(c)(2) of the PRA the labeling requirements in proposed §§ 1271.65(c)(2) and (d), and 1271.90(b) and (c) do not constitute collection of information because information required to be on the labeling is originally supplied by FDA to the manufacturers for the purpose of disclosure to the public to help ensure a safe product supply and protect public health.

The reporting of screening and testing results to the consignee in proposed § 1271.65(c)(4) does not constitute collection of information burden because it is the customary and usual practice or procedure of all manufacturers to conduct screening and testing and provide the results to the consignee.

In compliance with section 3507(d) of the PRA of 1995 (44 U.S.C. 3507(d)), the agency has submitted a copy of this proposed rule to OMB for review of the information collection provisions.

VI. Environmental Impact

The agency has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VII. Request for Comments and Proposed Effective Date

Interested persons may, on or before (*insert date 90 days after date of publication in the Federal Register*), submit to the Dockets Management Branch (address above) written comments regarding this proposal, except that comments regarding information collection provisions should be submitted in accordance with the instructions in section V of this document. Two copies of any comments on issues other than information collection are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

FDA is proposing to delay the compliance date of all final rules implementing the proposed regulatory approach to human cellular and tissue-based products until the concluding final rule for registration, donor suitability, and CGTP has been published in the **Federal Register**. FDA will announce the compliance date for the final rules in a future issue of the **Federal Register**.

VIII. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. CDC, 1995 *ART Fertility Clinic Reports* at “www.cdc.gov/nccdphp/drh/arts/introduc.htm”.
2. Published fee for blood testing, including Hepatitis B and Hepatitis C, HIV 1–2, HTLV–1, and syphilis, reported for direct donor screening by The Sperm Bank of California, at “www.thespermbankofca.org/fees96.htm”.

3. The Sperm Bank of California at “www.thespermbankofca.org/fees96.htm”.
4. Van Voorhis, B. J., A. E. T. Sparks, B. D. Allen, et al. “Cost-effectiveness of Infertility Treatments: A Cohort Study,” *Fertility and Sterility*, vol. 67, No. 5, May 1997, pp. 830–836.
5. Margolis, H. S., P. J. Coleman, R. E. Brown, E. E. Mast, S. H. Sheingold, and J. A. Arevalo, “Prevention of Hepatitis B Virus Transmission by Immunization: An Economic Analysis of Current Recommendations,” *Journal of the American Medical Association*, vol. 274, No. 15, 1995, pp. 1201–1208.
6. The National Summary of CDC 1995 ART Fertility Clinic Reports estimates that 11 percent of the ART therapy performed included ICSI at “www.cdc.gov/nccdphp/drh/arts/introduc.htm”.
7. Wortley, P. M., T. A. Hammett, and P. L. Fleming, “Donor Insemination and Human Immunodeficiency Virus Transmission,” *Obstetrics & Gynecology*, vol. 91, No. 4, 1998, pp. 515–518.
8. Sidhu, R. S., R. K. Sharma, S. Kachoria, C. Curtis, and A. Agarwal, “Reasons for Rejecting Potential Donors from a Sperm Bank Program,” *Journal of Assisted Reproduction and Genetics*, vol. 14, No. 6, 1997, pp. 354–360.
9. The American Fertility Society, “Guidelines for Therapeutic Donor Insemination: Sperm,” *Fertility and Sterility*, vol. 62, No. 5, November 1994, pp. 101s–104s.
10. Government Accounting Office, *Human Tissue Banks: FDA Taking Steps to Improve Safety, but Some Concerns Remain*, GAO/HEHS–98–25.
11. AuBuchon, J. P., J. D. Birkmeyer, and M. P. Busch, “Safety of the Blood Supply to the United States: Opportunities and Controversies,” *Annals of Internal Medicine*, vol. 127, No. 10, November 1997, vol. 127, No. 10.
12. Kaur, S., L. Rybicki, B. R. Bacon, J. L. Gollan, V. K. Rustgi, W. D. Carey and the National Hepatitis Surveillance Group, “Performance Characteristics and Results of a Large-Scale Screening Program for Viral Hepatitis and Risk Factors Associated with Exposure to Viral Hepatitis B and C: Results of the National Hepatitis Screening Survey,” *Hepatology*, vol. 24, No. 5, 1996, pp. 979–986.
13. Kane, M., “Epidemiology of Hepatitis B Infection in North America,” *Vaccine*, vol. 13, Supplement 1: 1995, pp. s16–s17.

14. Guinan, M. E., "Artificial Insemination by Donor: Safety and Secrecy," *Journal of the American Medical Association*, vol. 173, No. 11, March 1995, pp. 890–891.
15. U.S. Centers for Disease Control and Prevention, 1997.
16. Kim, W. R., J. J. Poterucha, J. E. Hermans, T. M. Therneau, E. R. Dickson, R. W. Evans, and J. B. Gross, Jr., "Cost-effectiveness of 6 and 12 Months of Interferon- α Therapy for Chronic Hepatitis C," *Annals of Internal Medicine*, vol. 127, No. 10, November 1997.
17. U.S. Small Business Administration, Table of Size Standards, March 1, 1996, Major Group 80—Health Services.
18. Prottas, J., "A study of the Tissue Procurement and Distribution System of the United States," Brandeis University, FDA/HRSA contract No. 240–090–0048, October 1995.
19. American Medical Association, *Socioeconomic Characteristics of Medical Practice*, Table 47, p. 150, 1994.
20. Hogan, R. N., et al., "Risk of Prion Disease Transmission From Ocular Donor Tissue Transplantation," *Cornea*, vol. 18, No. 1, pp. 2–11, 1999.

List of Subjects

21 CFR Part 210

Drugs, Packaging and containers.

21 CFR Part 211

Drugs, Labeling, Laboratories, Packaging and containers, Prescription drugs, Reporting and recordkeeping requirements, Warehouses.

21 CFR Part 820

Medical devices, Reporting and recordkeeping requirements.

21 CFR Part 1271

Human cellular and tissue-based products, Communicable diseases, HIV/AIDS, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, it is proposed to amend 21 CFR Chapter I as follows:

I. Parts 210, 211, and 820 are amended as follows:

PART 210—CURRENT GOOD MANUFACTURING PRACTICE IN MANUFACTURING, PROCESSING, PACKING, OR HOLDING OF DRUGS; GENERAL

1. The authority citation for 21 CFR part 210 is revised to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 355, 360b, 371, 374; 42 U.S.C. 216, 262, 263a, 264.

2. Section 210.1 is amended by adding paragraph (c) to read as follows:

§ 210.1 Status of current good manufacturing practice regulations.

* * * * *

(c) Owners and operators of establishments engaged in the recovery, screening, testing, processing, storage, labeling, packaging or distribution of human cellular or tissue-based products, as defined in § 1271.3(e) of this chapter, that are regulated as drugs under the act and/or biological products under section 351 of the Public Health Service Act are subject to the donor suitability and current good tissue practice procedures set forth in part 1271 subparts C and D of this chapter, in addition to the regulations in this part and in parts 211 through 226 of this chapter. Failure to comply with any regulation set forth in this part, in parts 211 through 226 of this chapter, in part 1271 subpart C of this chapter, or in part 1271 subpart D of this chapter shall render such a human cellular or tissue-based product adulterated under section 501(a)(2)(B) of the act, and such product, as well as the person who is responsible for the failure to comply, shall be subject to regulatory action.

3. Section 210.2 is revised to read as follows:

§ 210.2 Applicability of current good manufacturing practice regulations.

(a) The regulations in this part and in parts 211 through 226 of this chapter as they may pertain to a drug, in parts 600 through 680 of this chapter as they may pertain to a biological product for human use, and in part 1271 of this chapter as they may pertain to a human cellular or tissue-based product that is regulated as a drug and/or biological product shall be considered to supplement, not supersede, each other, unless the regulations explicitly provide otherwise. In the event that it is impossible to comply with all applicable regulations in these parts, the regulations specifically applicable to the drug in question shall supersede the more general.

(b) If a person engages in only some operations subject to the regulations in this part, in parts 211 through 226 of this chapter, in parts 600 through 680 of this chapter, and in part 1271 of this chapter, and not in others, that person need only comply with those regulations applicable to the operations in which he or she is engaged.

PART 211—CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS

4. The authority citation for 21 CFR part 211 is revised to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 355, 360b, 371, 374; 42 U.S.C. 216, 262, 263a, 264.

5. Section 211.1 is amended by revising paragraph (b) to read as follows:

§ 211.1 Scope.

* * * * *

(b) The current good manufacturing practice regulations in this chapter as they pertain to drug products, in parts 600 through 680 of this chapter, as they pertain to biological products for human use, and in part 1271 of this chapter, as they pertain to human cellular or tissue-based products that are regulated as drugs and/or biological products shall be considered to supplement,

not supersede, the regulations in this part unless the regulations explicitly provide otherwise. In the event it is impossible to comply with applicable regulations both in this part and in other parts of this chapter, in parts 600 through 680 of this chapter, or in part 1271 of this chapter, the regulation specifically applicable to the drug product in question shall supersede the regulation in this part.

* * * * *

PART 820—QUALITY SYSTEM REGULATION

6. The authority citation for 21 CFR part 820 is revised to read as follows:

Authority: 21 U.S.C. 351, 352, 360, 360c, 360d, 360e, 360h, 360i, 360j, 360l, 371, 374, 381, 383; 42 U.S.C. 216, 262, 263a, 264.

7. Section 820.1 is amended by adding two sentences to the end of paragraph (a)(1) and by revising the second sentence in paragraph (c) to read as follows:

§ 820.1 Scope.

(a) *Applicability.* (1) * * * Manufacturers of human cellular or tissue-based products, as defined in § 1271.3(e) of this chapter, that are regulated as medical devices under the act are subject to this part and are also subject to the donor-suitability procedures set forth in part 1271 subpart C of this chapter and current good tissue practice procedures in part 1271 subpart D of this chapter. In the event that it is impossible to comply with all applicable regulations in parts 820 and 1271 of this chapter, the regulations specifically applicable to the device in question shall supersede the more general.

* * * * *

(c) * * * The failure to comply with any applicable provision in this part or in part 1271 subpart C or D of this chapter renders a device adulterated under section 501(h) of the act. * * *

* * * * *

II. Part 1271 as proposed in the Federal Register of May 14, 1998 (63 FR 26744) is amended as follows:

PART 1271—HUMAN CELLULAR AND TISSUE-BASED PRODUCTS

1. The authority citation for 21 CFR part 1271 is revised to read as follows:

Authority: 42 U.S.C. 216, 243, 263a, 264, 271.

2. The heading for part 1271 is revised to read as set forth above.

3. Section 1271.1 is revised to read as follows:

§ 1271.1 Purpose and scope.

(a) *Purpose.* The purpose of this part, in conjunction with §§ 207.20(f), 210.1(c), 210.2, 807.20(e), and 820.1(a) of this chapter, is to establish procedures to prevent the introduction, transmission, and spread of communicable diseases and to create a unified registration and product listing system for establishments that manufacture human cellular and tissue-based products.

(b) *Scope.* Manufacturers of human cellular and tissue-based products regulated solely under the authority of section 361 of the Public Health Service Act (the PHS Act) are required by this part to register and list their products with the Food and Drug Administration's (FDA's) Center for Biologics Evaluation and Research, and to comply with the other requirements contained in this part. Under §§ 207.20(f) and 807.20(e), manufacturers of human cellular and tissue-based products regulated under section 351 of the PHS Act and/or the Federal Food, Drug, and Cosmetic Act (the act) are required to register and list their products following the procedures in subpart B of this part; under §§ 210.1(c), 210.2, 211.1(b), and 820.1(a), manufacturers of those products are required to comply with the donor-suitability procedures in subpart C of this part and current good tissue practice procedures in subpart D of this part in addition to all other applicable regulations.

4. Section 1271.3 is amended by revising paragraph (e), and by adding paragraphs (i) through (ee) to read as follows:

§ 1271.3 Definitions.

* * * * *

(e) *Human cellular or tissue-based product* means a product containing or consisting of human cells or tissues that is intended for implantation, transplantation, infusion, or transfer into a human recipient, e.g., cadaveric ligament, skin, dura mater, heart valve, cornea, hematopoietic stem cells derived from peripheral and cord blood, manipulated autologous chondrocytes, and spermatozoa.

The following products are not considered human cellular or tissue-based products:

(1) Vascularized human organs for transplantation;

(2) Whole blood or blood components or blood derivative products subject to listing under parts 607 and 207 of this chapter, respectively;

(3) Secreted or extracted human products, such as milk, collagen, and cell factors; except that semen is considered a human cellular or tissue-based product;

(4) Minimally manipulated bone marrow for homologous use and not combined with or modified by the addition of any component that is a drug or a device;

(5) Ancillary products used in the manufacture of cellular or tissue-based products;

(6) Cells, tissues, and organs derived from animals other than humans; and

(7) In vitro diagnostic products as defined in § 809.3(a) of this chapter.

* * * * *

(i) *Biohazard legend* appears on packaging as follows and is used to mark products that present a known or suspected relevant communicable disease risk.



BIOHAZARD

(j) *Blood component* means any part of human blood separated by physical or mechanical means.

(k) *Colloid* means:

(1) A protein or polysaccharide solution, such as albumin, dextran, or hetastarch, that can be used to increase or maintain osmotic (oncotic) pressure in the intravascular compartment; or

(2) Certain blood components such as plasma and platelets.

(l) *Crystalloid* means a balanced salt and/or glucose solution used for electrolyte replacement or to increase intravascular volume, such as saline solution, Ringer's lactate solution, or 5 percent dextrose in water.

(m) *Directed donor* means a living person who is the source of cells or tissue designated for a specific potential recipient of a human cellular or tissue-based product.

(n) *Donor* means a person, living or dead, who is the source of cells or tissue for a human cellular or tissue-based product.

(o) *Donor medical history interview* means a documented dialogue with the donor, if living or, if the donor is not living or is unable to participate in the interview, with an individual or individuals knowledgeable about the donor's medical history and relevant social behavior, such as the donor's next-of-kin, the nearest available relative, a member of the donor's household, an individual with an affinity relationship, and/or the primary treating physician. With respect to relevant social behavior, the interview includes questions about whether or not the donor met certain descriptions or engaged in activities or behaviors considered to place the donor at increased risk for a relevant communicable disease.

(p) *Embryo* means the product from fertilization of the oocyte to the 8th week of development.

(q) *Gamete* means a male or female germ cell; i.e., spermatocyte or oocyte.

(r) *Physical assessment* means a limited autopsy or recent antemortem or postmortem physical examination of the donor to assess for signs or symptoms of a relevant communicable disease and for signs or symptoms suggestive of any risk factor for such disease.

(s) *Plasma dilution* means a decrease in the concentration of the donor's plasma proteins and circulating antigens or antibodies resulting from the transfusion of blood or blood components and/or infusion of fluids.

(t) *Quarantine* means the storage or identification of a human cellular or tissue-based product, in order to prevent improper release, in a physically separate area clearly identified for such use, or through use of other procedures, such as automated designation.

(u) *Reconstituted blood* means the blood produced by the extracorporeal resuspension of a blood unit labeled as "Red Blood Cells" through the addition of colloids and/or crystalloids to produce a product with a hematocrit in the normal range.

(v) *Relevant medical records* means a collection of documents that includes a current donor medical history interview; a current report of the physical assessment of a cadaveric donor or the physical examination of a living donor; and, if available, the following:

- (1) Laboratory test results (other than results of testing for relevant communicable disease agents required under this subpart);
- (2) Medical records;
- (3) Coroner and autopsy reports; and
- (4) Records or other information received from any source pertaining to risk factors for relevant communicable disease (e.g., social behavior, clinical signs and symptoms of relevant communicable disease, and treatments related to medical conditions suggestive of risk for relevant communicable disease).

(w) *Responsible person* means a person who is authorized to perform designated functions for which he or she is trained and qualified.

(x) *Summary of records* means a condensed version of the records of required screening and testing and contains:

- (1) A statement that the communicable disease testing was performed by a laboratory or laboratories certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA);
- (2) A listing and interpretation of the results of all communicable disease tests performed;

(3) A statement describing the types of records which may have been reviewed as part of the relevant medical records; and

(4) The name and address of the establishment determining the suitability of the donor of cells or tissues.

(y) *Relevant communicable disease agent or disease* means:

(1) One of the following disease agents or diseases:

(i) Human immunodeficiency virus, types 1 and 2;

(ii) Hepatitis B virus;

(iii) Hepatitis C virus;

(iv) Human transmissible spongiform encephalopathies, including Creutzfeldt–Jakob disease;

(v) *Treponema pallidum*;

(vi) Human T-lymphotropic virus, types I and II;

(vii) Cytomegalovirus;

(viii) *Chlamydia trachomatis*; and

(ix) *Neisseria gonorrhea*.

(2) A disease agent or disease not listed in paragraph (z)(1) of this section:

(i) That is sufficiently prevalent among potential donors to warrant screening or testing of all donors;

(ii) For which there is a risk of transmission by a human cellular or tissue-based product, either to the recipient of the product or to those people who may handle or otherwise come in contact with the product, such as medical personnel;

(iii) That poses significant health risks, as measured by morbidity and mortality; and

(iv) For which appropriate screening measures have been developed and/or an appropriate screening test for donor specimens has been licensed, approved, or cleared for such use by FDA and is available.

(z) *Urgent medical need* means that no comparable human cellular or tissue-based product is available and the recipient is likely to suffer serious morbidity without the product.

(aa) *Xenotransplantation* means any procedure that involves the use of live cells, tissues, or organs from a nonhuman animal source, transplanted or implanted into a human, or used for ex vivo contact with human body fluids, cells, tissues, or organs that are subsequently given to a human recipient.

(bb) *Close contacts* means household members and others with whom the recipient participates in activities that could result in exchanges of bodily fluids.

(cc) *Act* means the Federal Food, Drug, and Cosmetic Act.

(dd) *PHS Act* means the Public Health Service Act.

(ee) *FDA* means the Food and Drug Administration.

5. Section 1271.10 is revised to read as follows:

§ 1271.10 Establishments subject to this part; criteria for regulation of human cellular and tissue-based products solely under section 361 of the PHS Act.

The owner or operator of an establishment, foreign or domestic, that manufactures a human cellular or tissue-based product, whether or not the product enters into interstate commerce, is required under this part to register with FDA, to submit to the agency a list of each human cellular or tissue-based product manufactured, and to comply with the other requirements of this part, if the product:

- (a) Is minimally manipulated;
- (b) Is not promoted or labeled for any use other than a homologous use;
- (c) Is not combined with or modified by the addition of any component that is a drug or a device; and
- (d)(1) Either does not have a systemic effect; or
- (2) Has a systemic effect, and—
 - (i) Is for autologous use;
 - (ii) Is for a family-related allogeneic use; or
 - (iii) Is for reproductive use.

6. Section 1271.15 is added to read as follows:

§ 1271.15 Criteria for regulation of human cellular and tissue-based products under the act and/or section 351 of the PHS Act.

Human cellular or tissue-based products that are regulated as drugs, devices and/or biological products under the act and/or section 351 of the PHS Act, and the establishments that manufacture those products, are subject to all applicable regulations in title 21, chapter 1. In conjunction with those regulations, the procedures in part 1271, subparts B, C, and D shall be followed, as specified in §§ 207.20(f), 210.1(c), 210.2, 211.1(b), 807.20(e), and 820.1(a) of this chapter. A human cellular or tissue-based product is regulated under the act and/or section 351 of the PHS Act if it:

- (a) Is more than minimally manipulated;
- (b) Is promoted or labeled for any use other than a homologous use;
- (c) Is combined with or modified by the addition of any component that is a drug or a device;

or

- (d) Has a systemic effect and—
 - (1) Is not for autologous use;
 - (2) Is not for a family-related allogeneic use; and
 - (3) Is not for reproductive use.

7. Section 1271.20 is revised to read as follows:

§ 1271.20 Establishments not required to comply with the requirements of this part.

The following establishments are not required to register, list, or meet the other requirements of this part:

- (a) Establishments that use human cellular or tissue-based products solely for nonclinical scientific or educational purposes;
- (b) Establishments that remove human cellular or tissue-based products from an individual and implant such cells or tissues into the same individual during the same surgical procedure;

(c) Carriers who accept, receive, carry, hold, or deliver human cellular or tissue-based products in the usual course of business as carriers;

(d) Establishments that do not, recover, screen, test, process, label, package, or distribute, but only receive or store human cellular or tissue-based products solely for pending scheduled implantation, transplantation, infusion, or transfer within the same facility.

8. Subpart C, consisting of §§ 1271.50 through 1271.90, is added to read as follows:

Subpart C—Donor Suitability

Sec.

1271.50 Determination of donor suitability.

1271.55 Records of donor suitability determination.

1271.60 Quarantine pending determination of donor suitability.

1271.65 Quarantine and disposition of human cellular or tissue-based product from a donor determined to be unsuitable.

1271.75 Donor screening.

1271.80 Donor testing; general requirements.

1271.85 Donor testing; specific requirements.

1271.90 Exceptions from the requirement of donor suitability determination; labeling requirements.

Subpart C—Donor Suitability

§ 1271.50 Determination of donor suitability.

(a) Except as provided under §§ 1271.65 and 1271.90 of this subpart, a human cellular or tissue-based product shall not be implanted, transplanted, infused, or transferred until the donor of the cells or tissue for the product has been determined to be suitable. In the case of an embryo, donor suitability shall be determined for both the oocyte donor and the sperm donor.

(b) Donor suitability shall be determined and documented by a responsible person as defined in § 1271.3(w).

(c) A determination that a donor is suitable or unsuitable shall be based upon the results of donor screening in accordance with § 1271.75 and donor testing in accordance with §§ 1271.80 and 1271.85.

(d) A donor may be determined to be suitable if:

(1) The results of donor screening in accordance with § 1271.75 indicate that the donor is free from risk factors for and clinical evidence of infection due to relevant communicable disease agents and diseases and is neither a xenotransplant recipient nor a close contact of a xenotransplant recipient; and

(2) The results of donor testing for relevant communicable disease agents in accordance with §§ 1271.80 and 1271.85 are negative or nonreactive.

§ 1271.55 Records of donor suitability determination.

(a) A human cellular or tissue-based product from a donor determined to be suitable or from a donor determined to be unsuitable and made available for use under the provisions of § 1271.65(b), (c), or (d) shall be accompanied by documentation of the donor-suitability determination required by § 1271.50 from which the donor's name has been deleted. This documentation shall include:

(1)(i) A copy of the donor's relevant medical records, as defined in § 1271.3(v), results of testing required under §§ 1271.80 and 1271.85, and the name and address of the establishment that made the donor-suitability determination; or

(ii) A summary of records, as defined in § 1271.3(x); and

(2) A statement whether, based on the results of donor screening and testing, the donor has been determined to be suitable or unsuitable.

(b) The establishment that generates records used in determining donor suitability and the establishment that makes the donor-suitability determination shall retain such records and shall make them available for authorized inspection by or upon request from FDA. Records that can be readily retrieved from another location by electronic means are considered "retained." Records

shall be retained at least 10 years after the date of implantation, transplantation, infusion, or transfer of the product, or if the date of implantation, transplantation, infusion, or transfer is not known, then records shall be retained at least 10 years after the date of the product's distribution, disposition, or expiration, whichever is latest.

§ 1271.60 Quarantine pending determination of donor suitability.

(a) A human cellular or tissue-based product shall be kept in quarantine, as defined in § 1271.3(t), until completion of the donor-suitability determination required by § 1271.50. For reproductive cells and tissues that can reliably be stored, quarantine shall last until completion of the testing required under § 1271.85(d).

(b) A human cellular or tissue-based product in quarantine pending completion of a donor-suitability determination shall be clearly identified as in quarantine and shall be easily distinguishable from products that are available for release and distribution.

(c) A human cellular or tissue-based product shipped before it is available for release or distribution shall be kept in quarantine and shall be accompanied by records identifying the donor (e.g., by donor number), stating that the donor-suitability determination has not been completed, and stating that the product may not be implanted, transplanted, infused, or transferred until completion of the donor-suitability determination.

§ 1271.65 Quarantine and disposition of human cellular or tissue-based product from a donor determined to be unsuitable.

(a) If the donor of the cells or tissue for a human cellular or tissue-based product is determined to be unsuitable based on the results of required testing and/or screening, the product shall be kept in quarantine and physically separated from all other products until destruction or other disposition in accordance with paragraph (b) or (c) of this section is accomplished.

(b)(1) Except as provided in paragraph (b)(4) of this section, a human cellular or tissue-based product from a donor who has been determined to be unsuitable, based on the results of required

testing and/or screening, is not prohibited by this subpart C of this part from use for implantation, transplantation, infusion, or transfer under the following circumstances:

- (i) The product is for family-related, allogeneic use, as defined in § 1271.3(c);
- (ii) The product contains reproductive tissue from a directed donor, as defined in § 1271.3(m);

or

- (iii) There is a documented urgent medical need as defined in § 1271.3(aa).

(2) A human cellular or tissue-based product made available for use under the provisions of paragraph (b)(1) of this section shall be labeled with the Biohazard legend shown in § 1271.3(i).

(3) The manufacturer of a human cellular or tissue-based product used under the provisions of paragraph (b)(1) of this section shall document that:

- (i) The physician using the product was notified of the results of testing and screening;
- (ii) The physician authorized the use of the product;

(iii) The physician agreed to explain the communicable disease risks associated with the use of the product to the recipient or the recipient's legally authorized representative; and

(iv) The physician agreed to obtain from the recipient or the recipient's legally authorized representative consent to use the product.

(4) A human cellular or tissue-based product from a donor who is identified under § 1271.75(a)(2) as either having received a xenotransplant or having been a close contact of a xenotransplant recipient shall not be made available for use under the provisions of paragraph (b)(1) of this section.

(c)(1) A human cellular or tissue-based product from a donor for whom the donor-suitability determination has not yet been completed is not prohibited by this subpart C from use for implantation, transplantation, infusion, or transfer if there is a documented urgent medical need as defined in § 1271.3(z).

(2) A human cellular or tissue-based product made available for use under the provisions of paragraph (c)(1) of this section shall be labeled "NOT EVALUATED FOR INFECTIOUS SUBSTANCES" and shall be accompanied by a statement of:

(i) The results of donor screening required under § 1271.75, if complete;

(ii) The results of any testing required under § 1271.80 or § 1271.85 that has been completed;

and

(iii) A list of any testing required under § 1271.80 or § 1271.85 that has not yet been completed.

(3) The manufacturer of a human cellular or tissue-based product used under the provisions of paragraph (c)(1) of this section shall document that:

(i) The physician using the product was notified that the testing and screening were not complete;

(ii) The physician authorized the use of the product after determining there is an urgent medical need;

(iii) The physician agreed to explain the communicable disease risks associated with the use of the product to the recipient or the recipient's legally authorized representative; and

(iv) The physician agreed to obtain from the recipient or the recipient's legally authorized representative consent to use the product.

(4) In the case of a human cellular or tissue-based product used under the provisions of paragraph (c)(1) of this section, the donor-suitability determination shall be completed during or after the emergency use of the product, and the manufacturer shall inform the physician of the results of the determination.

(d) A human cellular or tissue-based product from a donor who has been determined to be unsuitable, based on the results of required testing and/or screening, is not prohibited by this subpart C of this part from use for nonclinical purposes, provided that it is labeled:

(1) "For Nonclinical Use Only"; and

(2) With the Biohazard legend shown in § 1271.3(i).

§ 1271.75 Donor screening.

(a)(1) Except as provided under § 1271.90, the relevant medical records of a donor of cells or tissue for a human cellular or tissue-based product shall be reviewed for risk factors for and clinical evidence of relevant communicable disease agents and diseases including, at a minimum, the following:

- (i) Human immunodeficiency virus;
- (ii) Hepatitis B virus;
- (iii) Hepatitis C virus; and
- (iv) Human transmissible spongiform encephalopathies including Creutzfeldt–Jakob disease.

(2) Except as provided under § 1271.90, the relevant medical records of a donor of cells or tissue for a human cellular or tissue-based product shall be reviewed to determine whether the donor has received a xenotransplant or has been a close contact of a xenotransplant recipient.

(b) Except as provided under § 1271.90, the relevant medical records of a donor of reproductive cells or tissue shall be reviewed for risk factors for and clinical evidence of infection due to relevant sexually transmitted and genitourinary diseases that can be transmitted with the recovery of the reproductive cells or tissue including at a minimum *Chlamydia trachomatis* and *Neisseria gonorrhea*, in addition to the relevant communicable disease agents and diseases for which screening is required under paragraph (a) of this section.

(c) A donor who is identified as having risk factors for or clinical evidence of any of the relevant communicable disease agents or diseases for which screening is required under paragraph (a)(1) or (b) of this section, or is identified under paragraph (a)(2) of this section as either a xenotransplant recipient or a close contact of a xenotransplant recipient, shall be determined to be unsuitable.

(d) An abbreviated donor screening procedure that determines and documents any changes in the donor's medical history including relevant social behavior since the previous donation that would make the donor unsuitable may be used for a living donor of human cellular and tissue-

based products on subsequent donations. An abbreviated donor screening procedure may be used only when a complete donor screening procedure has been performed within the previous 6 months.

§ 1271.80 Donor testing; general requirements.

(a) To adequately and appropriately reduce the risk of transmission of relevant communicable diseases, and except as provided under § 1271.90, a donor specimen shall be tested for evidence of infection due to relevant communicable disease agents in accordance with paragraph (c) of this section. At a minimum, testing shall be performed for those relevant communicable disease agents specified in § 1271.85. In the case of a fetal or neonatal donor, a specimen from the mother is generally acceptable for testing.

(b) Except as provided in paragraphs (d)(2) and (d)(3) of this section, the donor specimen shall be collected at the time of recovery of cells or tissue from the donor or within 48 hours after recovery, except that the specimen from a living donor may be collected up to 7 days prior to recovery if:

(1) Recovery of the cells or tissue involves invasive procedures or substantial risk to the donor;

(2) Implantation, transplantation, infusion, or transfer of the recovered cells or tissue is necessary before results of testing performed on a specimen collected at the time of recovery or post recovery would be available; or

(3) Extensive processing of the recovered cells or tissue is necessary before results of testing performed on a specimen collected at the time of recovery or post recovery would be available.

(c) Testing shall be performed using appropriate FDA-licensed, approved, or cleared donor screening tests in accordance with the manufacturer's instructions to adequately and appropriately reduce the risk of transmission of relevant communicable disease agents or diseases; provided that, until such time as appropriate FDA-licensed, approved, or cleared donor screening tests for *Chlamydia trachomatis* and for *Neisseria gonorrhea* are available, FDA-licensed, approved, or cleared tests labeled for the detection of those organisms in an asymptomatic, low-prevalence

population shall be used. Tests specifically labeled for cadaveric specimens shall be used instead of a more generally labeled test when applicable and when available. Testing shall be performed by a laboratory certified to perform testing on human specimens under the CLIA.

(d) The following donors shall be determined to be unsuitable:

(1) A donor whose specimen tests repeatedly reactive or positive on a test for a relevant communicable disease agent in accordance with § 1271.85, except for:

(i) A donor whose specimen tests repeatedly reactive for cytomegalovirus (CMV) and additional testing does not show the presence of an active infection, or

(ii) A donor whose specimen tests reactive on a non-Treponemal screening test for syphilis and negative on a specific Treponemal confirmatory test;

(2) A donor from whom blood loss is known or suspected to have occurred and who received a transfusion or infusion of more than 2,000 milliliters (mL) of blood (i.e., whole blood, reconstituted blood, or red blood cells) or colloids within 48 hours, or more than 2,000 mL of crystalloids within 1 hour, or any combination thereof prior to the collection of a specimen from the donor for testing, unless:

(i) A specimen taken from the donor after blood loss but before the transfusion or infusion is available for relevant communicable disease testing; or

(ii) An algorithm designed to ensure that plasma dilution sufficient to affect test results has not occurred is utilized to evaluate the volumes administered in the 48 hours prior to collecting the specimen from the donor;

(3) A donor who is 12 years of age or younger and has received any transfusion of blood, colloids, and/or crystalloids prior to the recovery of the cells or tissue, unless:

(i) A specimen taken from the donor before the transfusion or infusion is available for relevant communicable disease testing; or

(ii) An algorithm designed to ensure that plasma dilution sufficient to affect test results has not occurred is utilized to evaluate the volumes administered in the 48 hours prior to collecting the specimen from the donor.

§ 1271.85 Donor testing; specific requirements.

(a) To adequately and appropriately reduce the risk of transmission of relevant communicable diseases, and except as provided under § 1271.90, a specimen from a donor of viable or nonviable cells or tissue for a human cellular or tissue-based product shall be tested for evidence of infection due to relevant communicable disease agents including, at a minimum, the communicable disease agents listed as follows.

- (1) Human immunodeficiency virus, type 1;
- (2) Human immunodeficiency virus, type 2;
- (3) Hepatitis B virus;
- (4) Hepatitis C virus; and
- (5) *Treponema pallidum*.

(b) To adequately and appropriately reduce the risk of transmission of relevant communicable diseases, and except as provided under § 1271.90, a specimen from a donor of viable, leukocyte-rich cells or tissue shall be tested for evidence of infection due to the relevant cell-associated communicable disease agents including, at a minimum, the communicable disease agents listed as follows, in addition to the relevant communicable disease agents for which testing is required under paragraph (a) of this section.

- (1) Human T-lymphotropic virus, type I;
- (2) Human T-lymphotropic virus, type II; and
- (3) Cytomegalovirus.

(c) To adequately and appropriately reduce the risk of transmission of relevant communicable diseases, and except as provided under § 1271.90, a specimen from a donor of reproductive cells or tissue shall be tested for evidence of infection due to relevant genitourinary disease agents.

Testing shall include, at a minimum, the communicable disease agents listed in paragraphs (c)(1) and (c)(2) of this section, in addition to the relevant communicable disease agents for which testing is required under paragraphs (a) and (b) of this section. However, if the reproductive cells or tissue are procured by a method that ensures freedom from contamination of the cells or tissue by

infectious disease organisms that may be present in the genitourinary tract, then tests for the communicable disease agents listed in paragraphs (c)(1) and (c)(2) of this section are not required.

Minimum testing for genitourinary disease agents include:

(1) *Chlamydia trachomatis*; and

(2) *Neisseria gonorrhea*.

(d) Except as provided under § 1271.90, at least 6 months after the date of donation of reproductive cells or tissue that can be reliably stored, a new specimen shall be taken from the donor and retested for evidence of infection due to the relevant communicable disease agents for which testing is required under paragraphs (a), (b), and (c) of this section.

(e) For donors of dura mater, an assessment designed to detect evidence of transmissible spongiform encephalopathy shall be performed.

§ 1271.90 Exceptions from the requirement of donor suitability determination; labeling requirements.

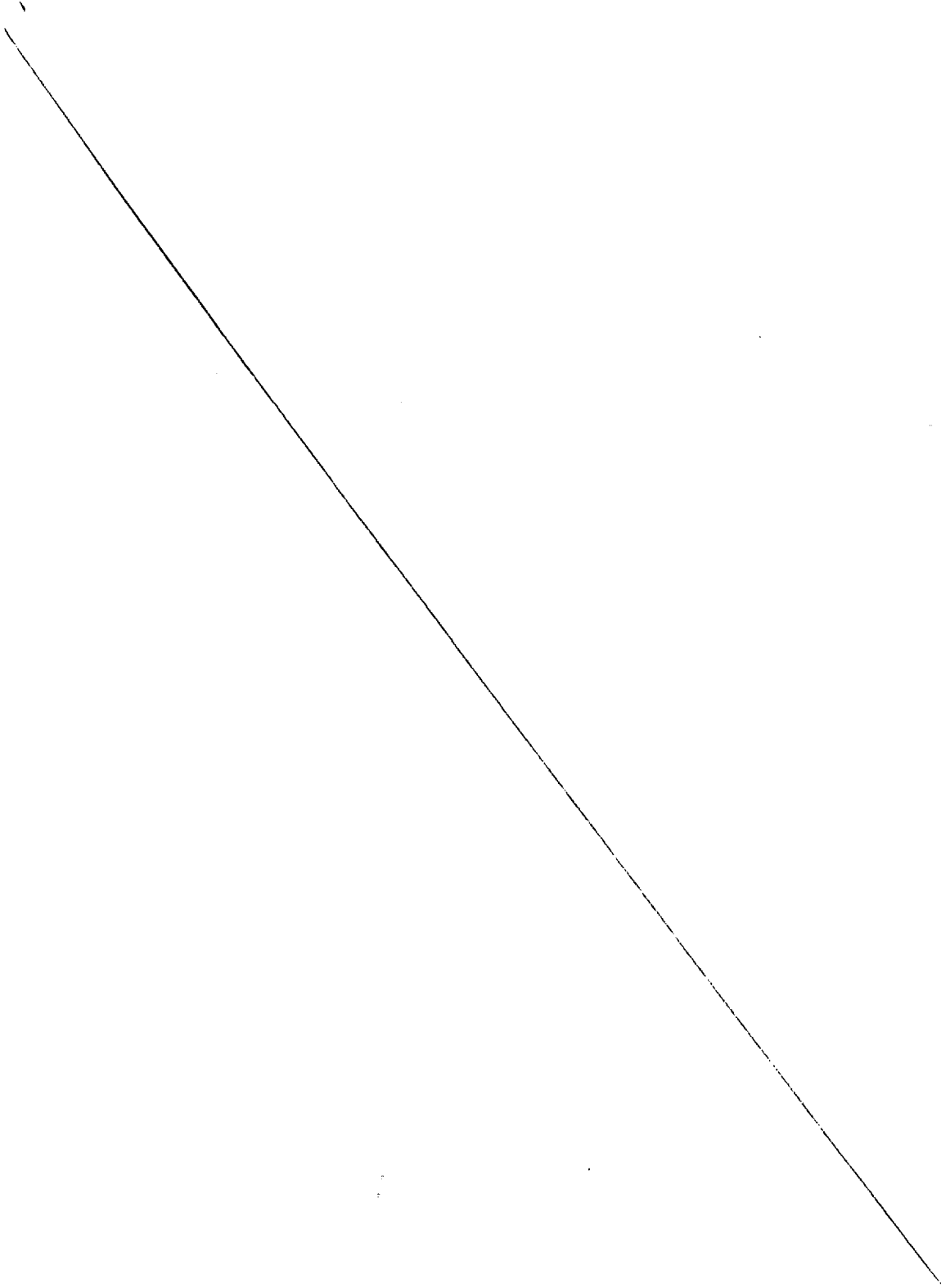
(a) For the following human cellular and tissue-based products, a determination of donor suitability under § 1271.50 is not required, and donor screening under § 1271.75, and testing under §§ 1271.80 and 1271.85 are recommended but not required:

(1) Banked cells and tissues for autologous use;

(2) Reproductive cells or tissue donated by a sexually-intimate partner of the recipient for reproductive use.

(b) If all screening and testing applicable to a comparable human cellular or tissue-based product under §§ 1271.75, 1271.80, and 1271.85 are not performed on the donor of a human cellular or tissue-based product listed in paragraph (a) of this section, the product shall be labeled “NOT EVALUATED FOR INFECTIOUS SUBSTANCES.” If any screening or testing is performed on a donor of a human cellular or tissue-based product listed in paragraph (a) of this section, and the results indicate the presence of relevant communicable disease agents and/or risk factors for

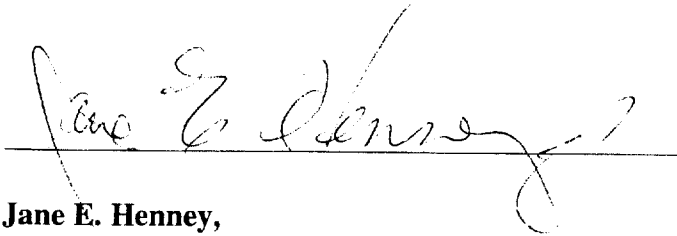
or clinical evidence of relevant communicable disease agents or diseases, the product shall be labeled with the Biohazard legend shown in § 1271.3(i).



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(c) Banked cells and tissues for autologous use shall be labeled "FOR AUTOLOGOUS USE ONLY."

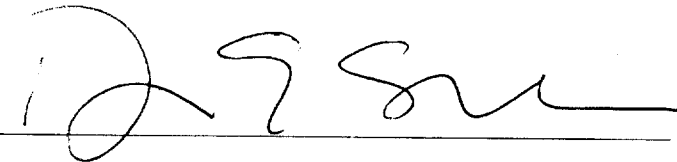
Dated: 2-19-99



Jane E. Henney,

Commissioner of Food and Drugs.

Dated: 8/29/99



Donna E. Shalala,

Secretary of Health and Human Services.

[FR Doc. 98-???? Filed ??-??-98; 8:45 am]

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